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(54) ELECTRICAL DEVICES AND ANTI-SCARRING AGENTS

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(60) Provisional application No. 60/586,861, filed on Jul. 9, 2004. Provisional application No. 60/578,471, filed on Jun. 9, 2004. Provisional application No. 60/526,541, filed on Dec. 3, 2003. Provisional application No. 60/525,226, filed on Nov. 24, 2003. Provisional application No. 60/523,908, filed on Nov. 20, 2003. Provisional application No. 60/524,023, filed on Nov. 20, 2003.

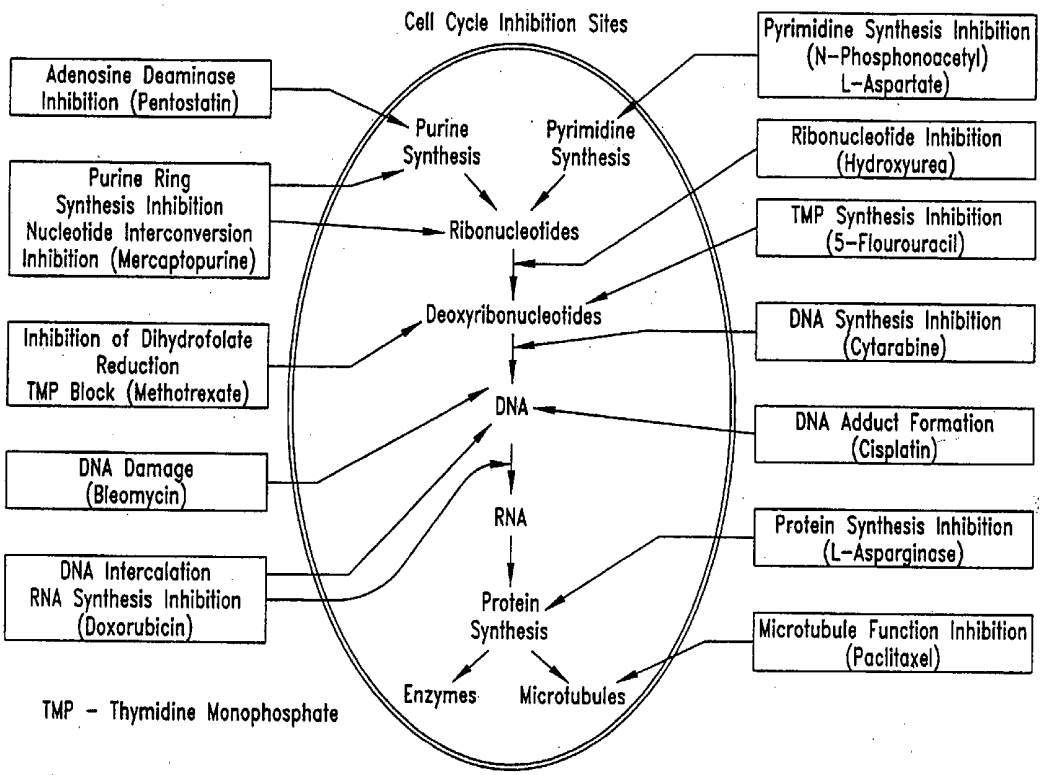
Publication Classification

(51) **Int. Cl.**[7] **A61N 1/05**

(52) **U.S. Cl.** **607/116**

(57) **ABSTRACT**

Electrical devices (e.g., cardiac rhythm management and neurostimulation devices) for contact with tissue are used in combination with an anti-scarring agent (e.g., a cell cycle inhibitor) in order to inhibit scarring that may otherwise occur when the devices are implanted within an animal.



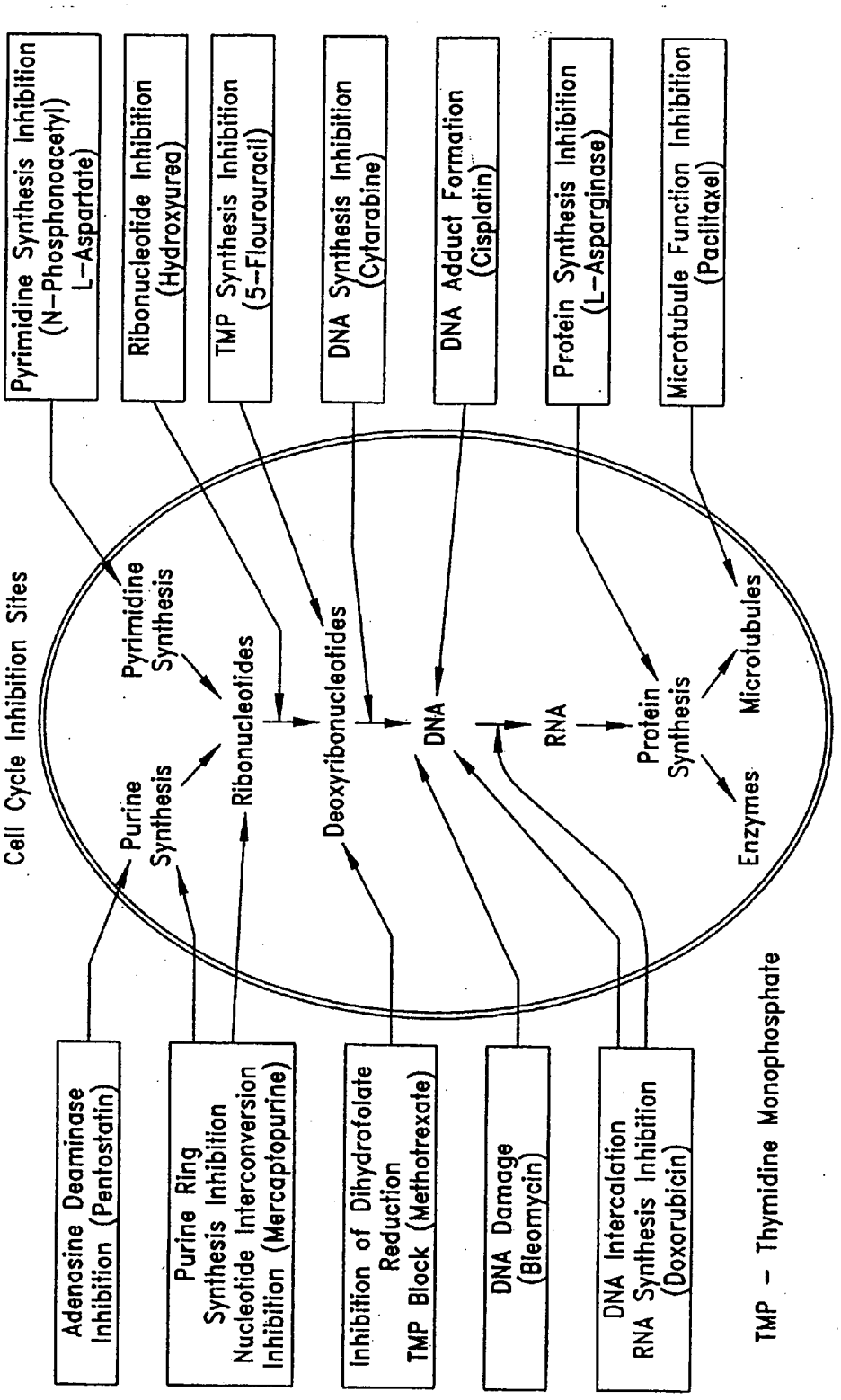

Cell Cycle Inhibition Sites
Pyrimidine Synthesis Inhibition (N-Phosphonoacetyl) L-Aspartate)
Ribonucleotide Inhibition (Hydroxyurea)
TMP Synthesis Inhibition (5-Flourouracil)
DNA Synthesis Inhibition (Cytarabine)
DNA Adduct Formation (Cisplatin)
Protein Synthesis Inhibition (L-Asparginase)
Microtubule Function Inhibition (Paclitaxel)
Pyrimidine Synthesis
Purine Synthesis
Ribonucleotides
Deoxyribonucleotides
DNA
RNA
Protein Synthesis
Microtubules
Enzymes
Adenosine Deaminase Inhibition (Pentostatin)
Purine Ring Synthesis Inhibition Nucleotide Interconversion Inhibition (Mercaptopurine)
Inhibition of Dihydrofolate Reduction TMP Block (Methotrexate)
DNA Damage (Bleomycin)
DNA Intercalation RNA Synthesis Inhibition (Doxorubicin)
TMP - Thymidine Monophosphate

Fig. 1

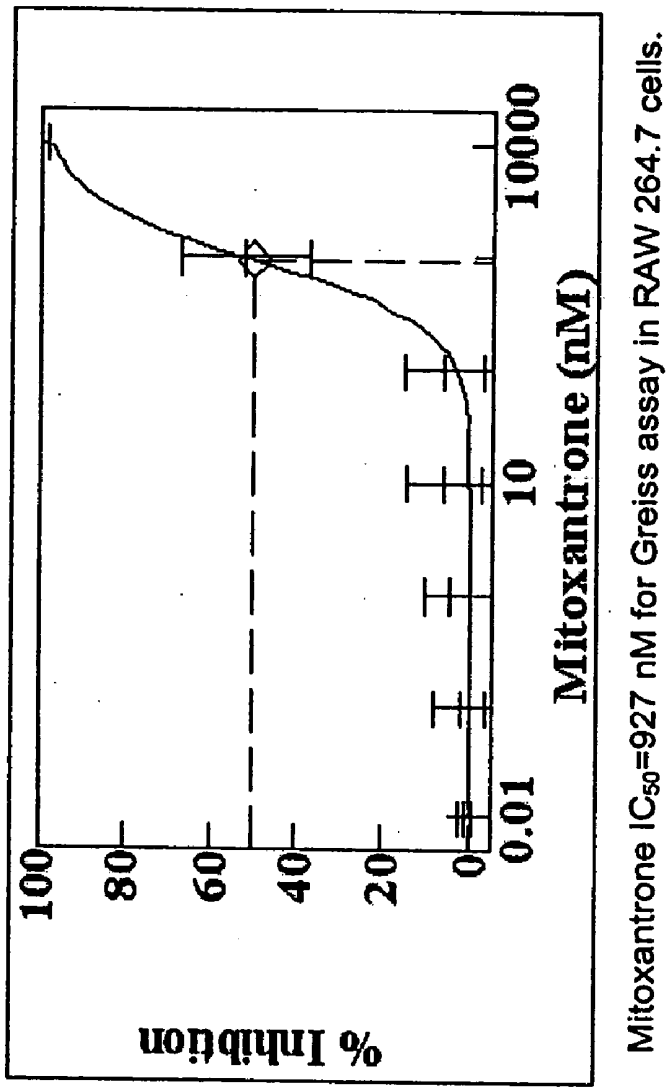
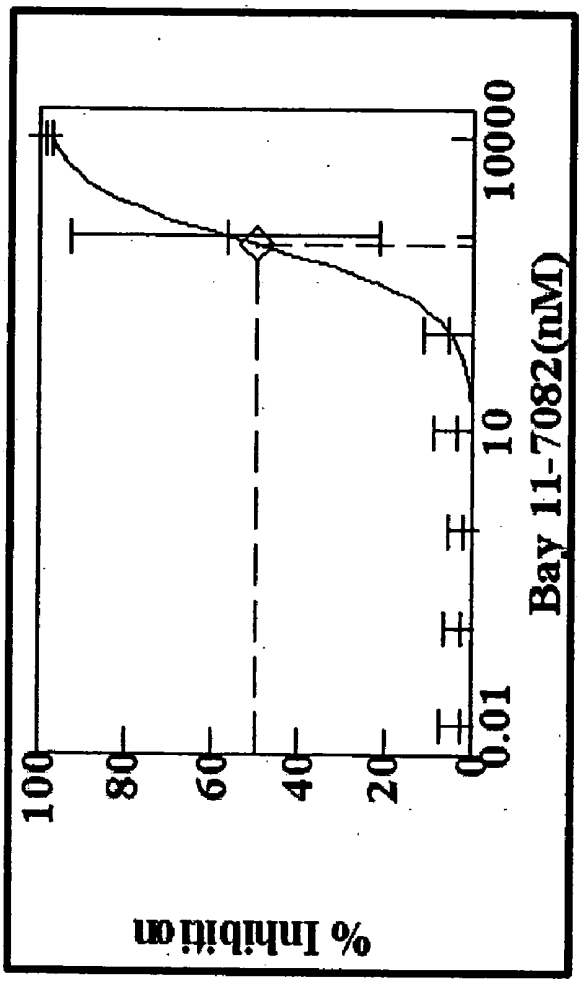
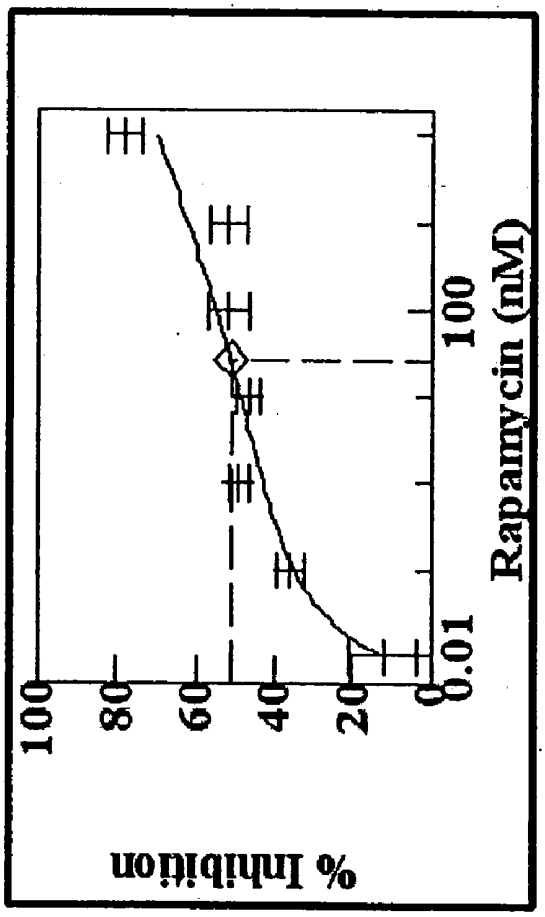

% Inhibition
100
80
60
40
20
0
0.01
10
10000
Mitoxantrone (nM)
Mitoxantrone IC50=927 nM for Greiss assay in RAW 264.7 cells.

Fig. 2



Bay 11-7082 IC_{50}=810 nM TNFα production by THP-1 cells.

Fig. 3



Rapamycin IC_{50}= 51 nM TNFα production by THP-1 cells.

Fig. 4

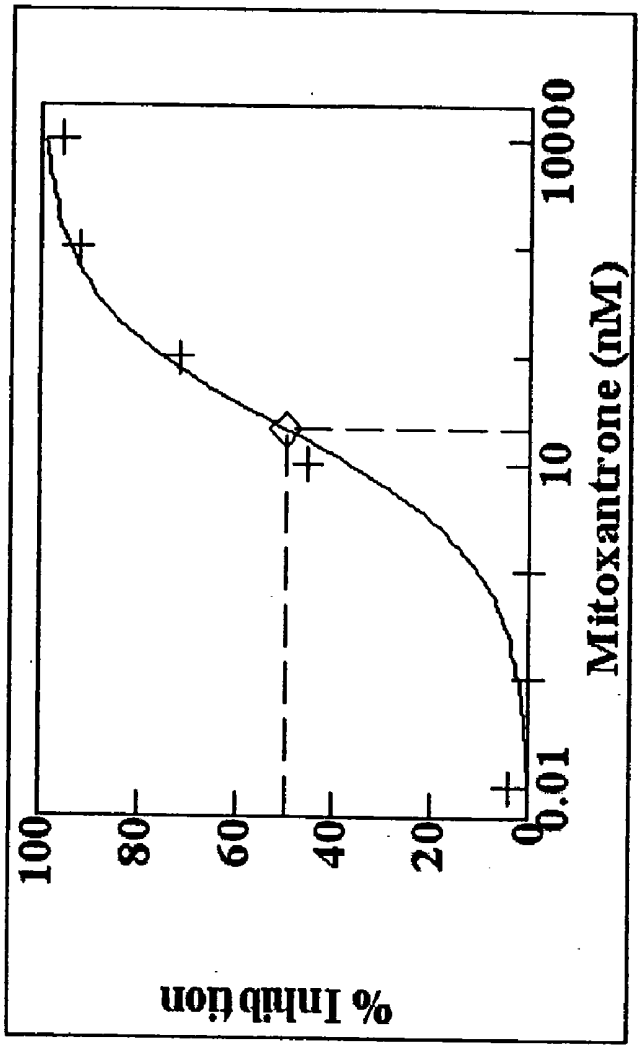
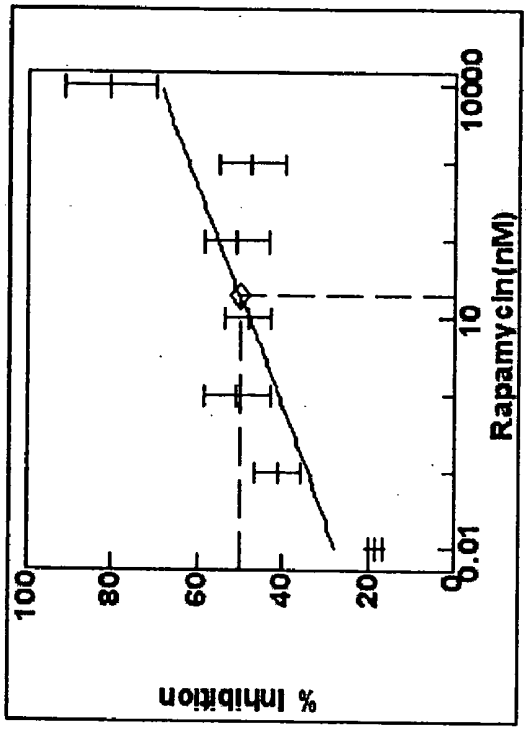
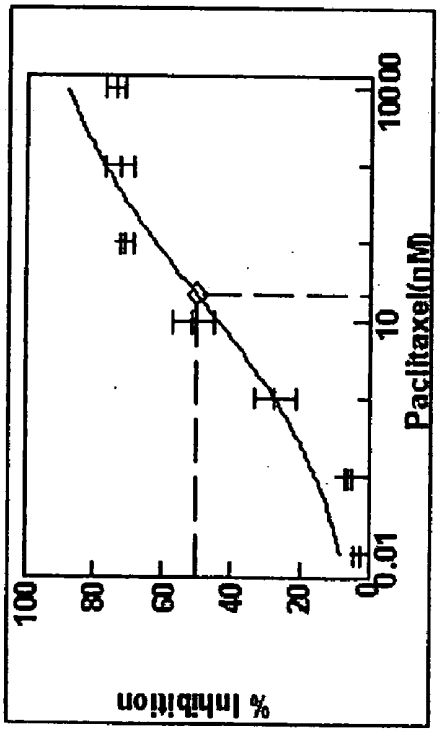


Fig. 5



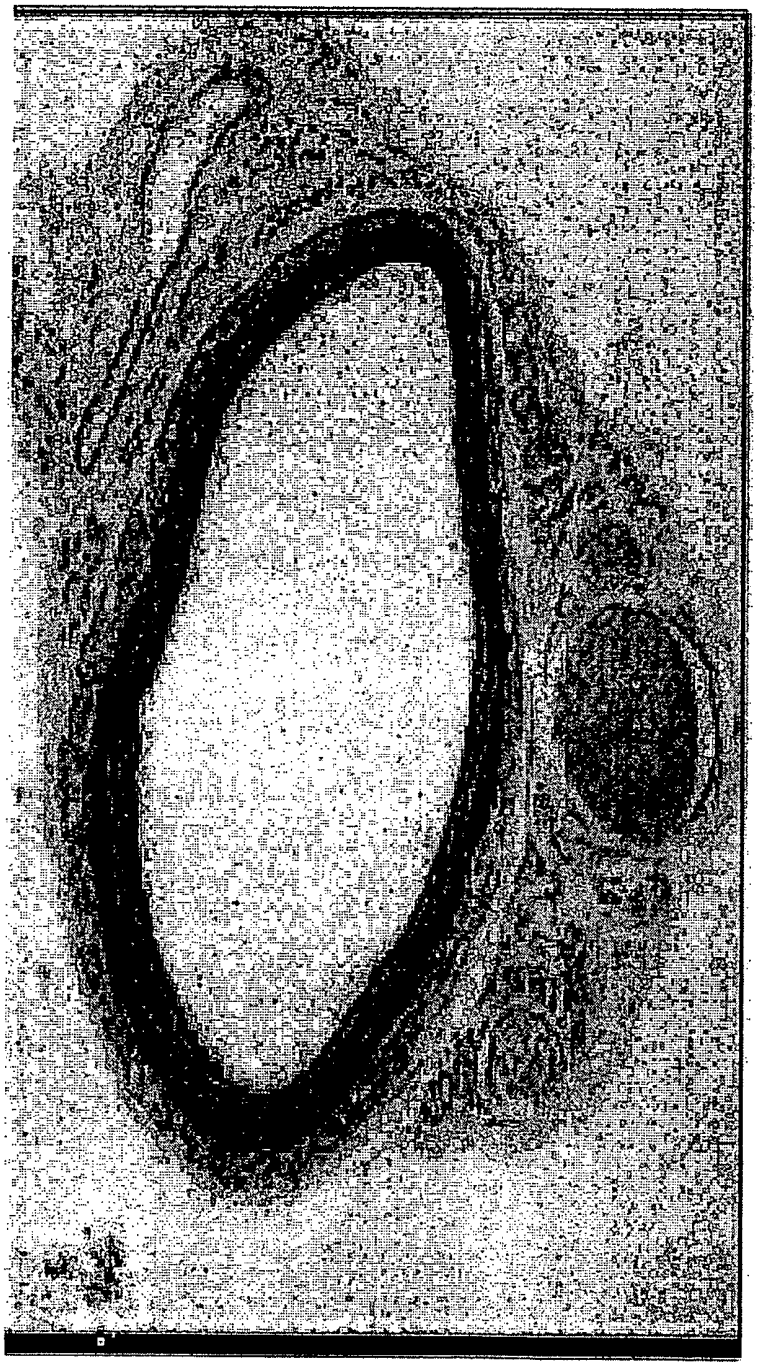
Rapamycin IC_{50}=19 nM for proliferation of human fibroblasts.

Fig. 6



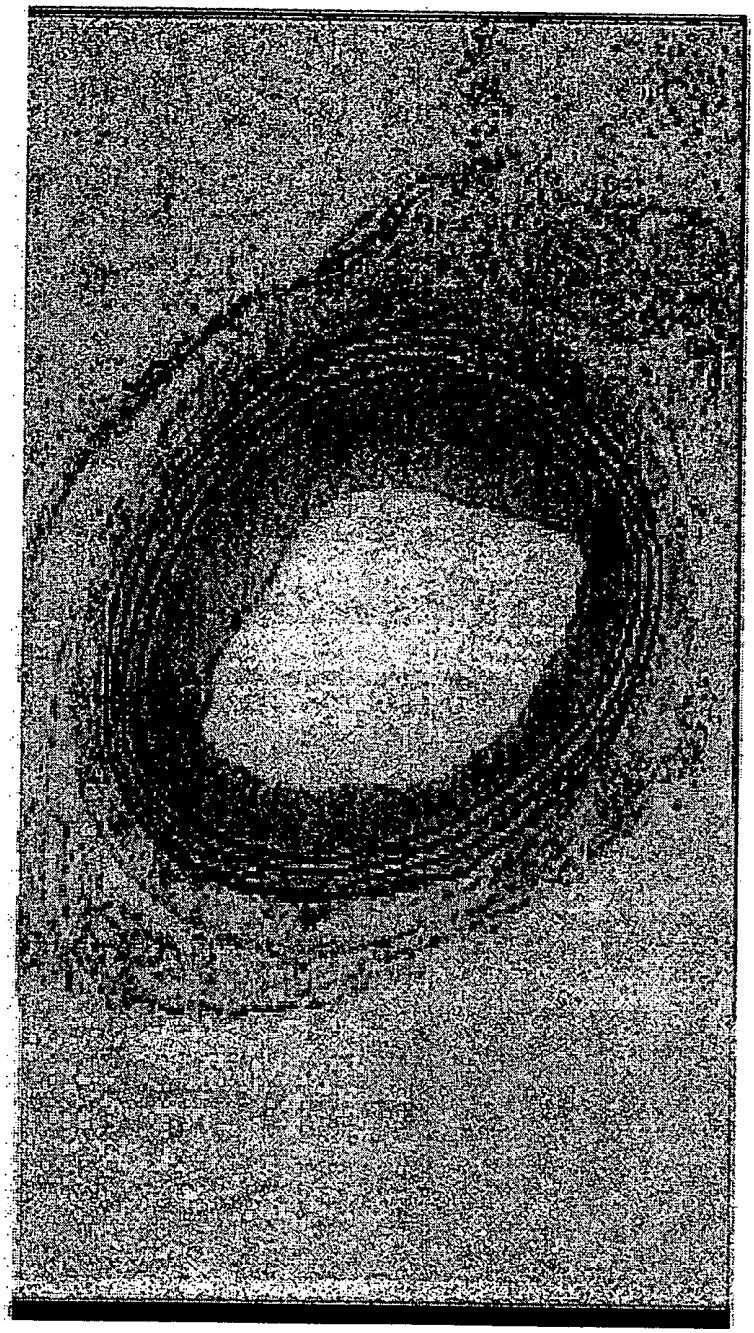
Paclitaxel IC_{50}=23 nM for proliferation of human fibroblasts.

Fig. 7



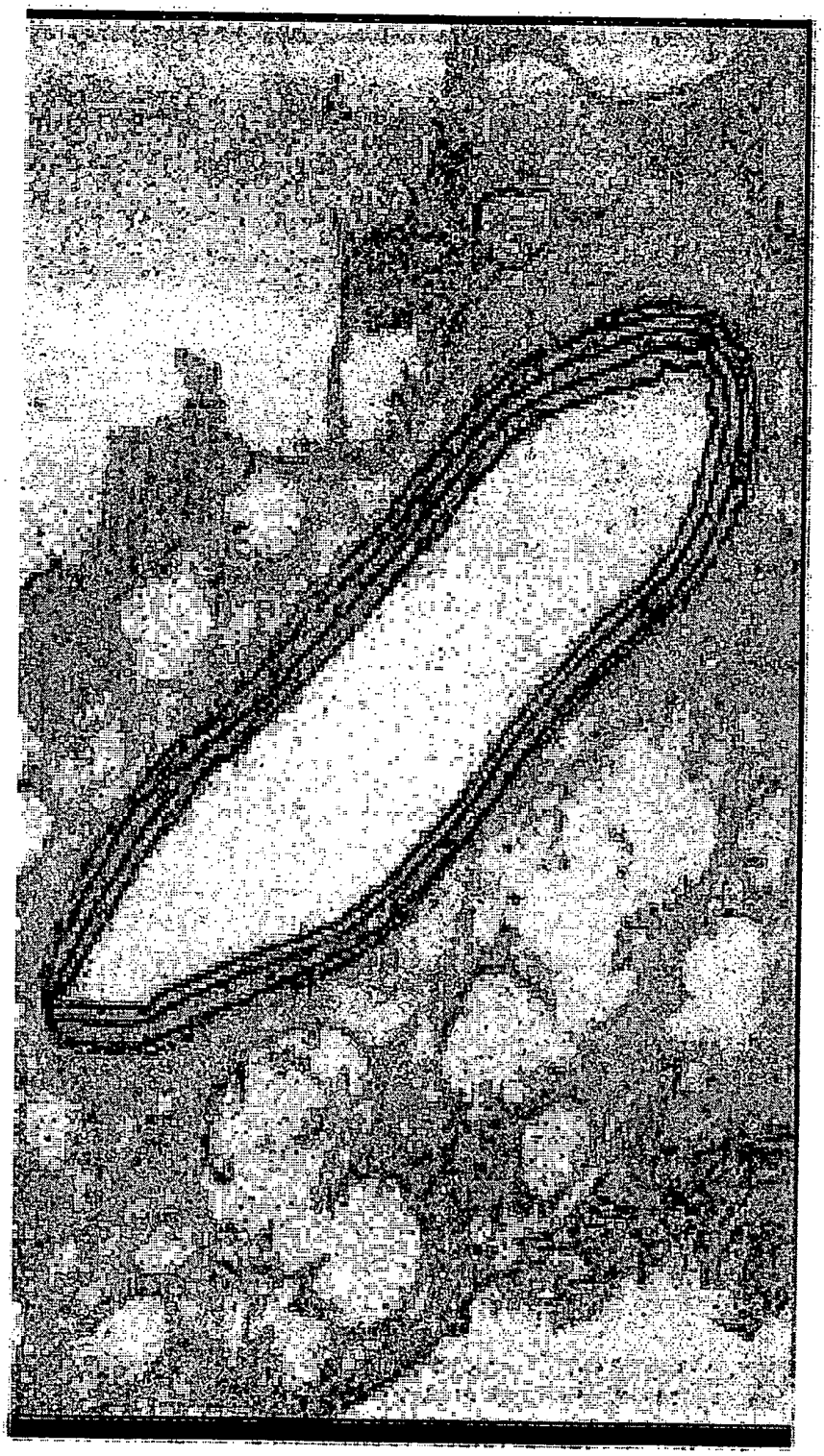
Uninjured carotid artery - Rat balloon injury model

Fig. 8



Control injured carotid artery - Rat balloon injury model

Fig. 9



Paclitaxel/mesh treated carotid artery - Rat balloon injury model (345 ug paclitaxel in a 50:50 PLG coating on a 10:90 PLG mesh)

Fig. 10

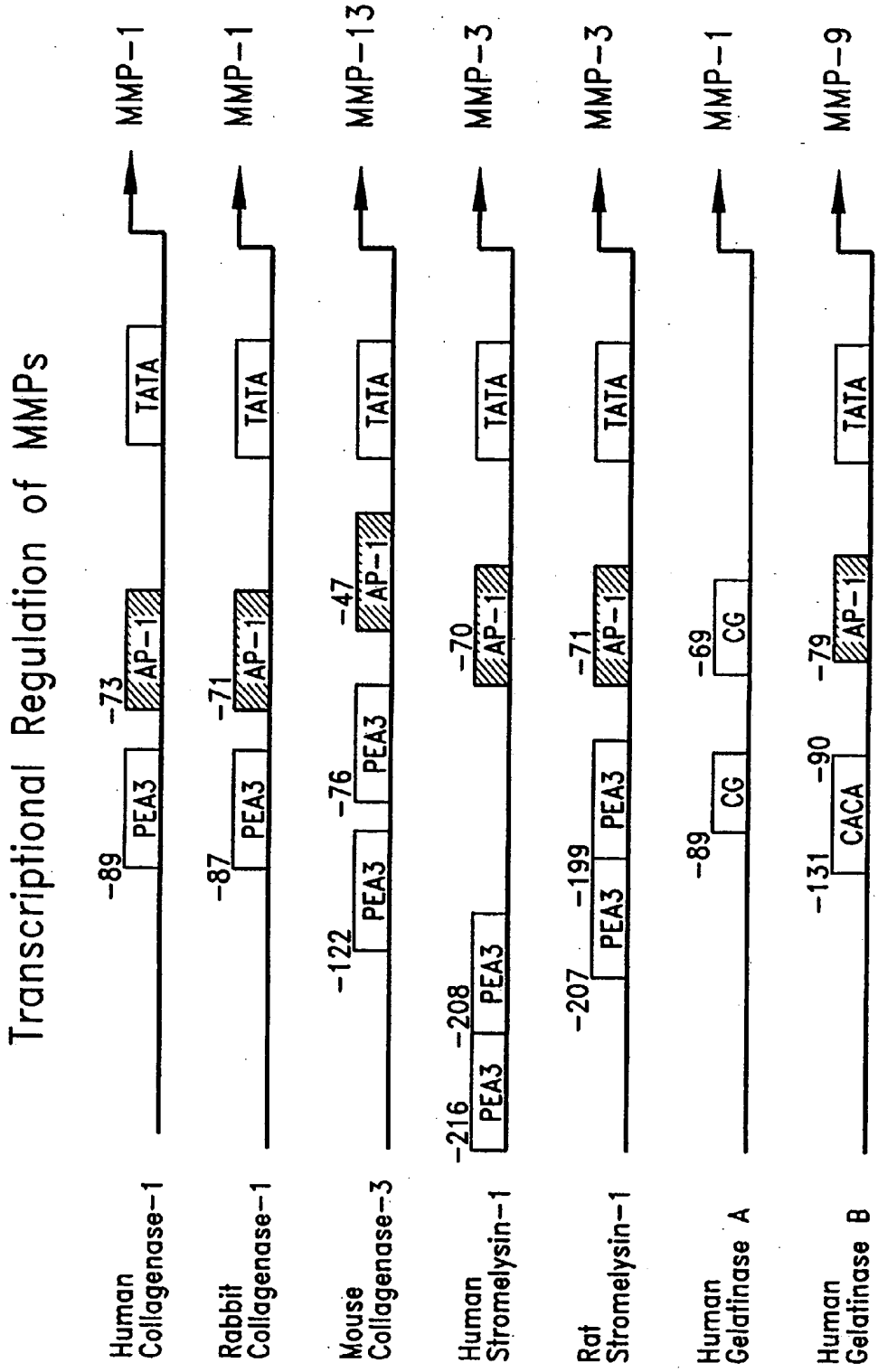

Transcriptional Regulation of MMPs
Human Collagenase-1
-89
PEA3
-73
AP-1
TATA
MMP-1
Rabbit Collagenase-1
-87
PEA3
-71
AP-1
TATA
MMP-1
Mouse Collagenase-3
-122
PEA3
-76
PEA3
-47
AP-1
TATA
MMP-13
Human Stromelysin-1
-216
PEA3
-208
PEA3
-70
AP-1
TATA
MMP-3
Rat Stromelysin-1
-207
PEA3
-199
PEA3
-71
AP-1
TATA
MMP-3
Human Gelatinase A
-89
CG
-69
CG
MMP-1
Human Gelatinase B
-131
CACA
-90
-79
AP-1
TATA
MMP-9

Fig. 11A

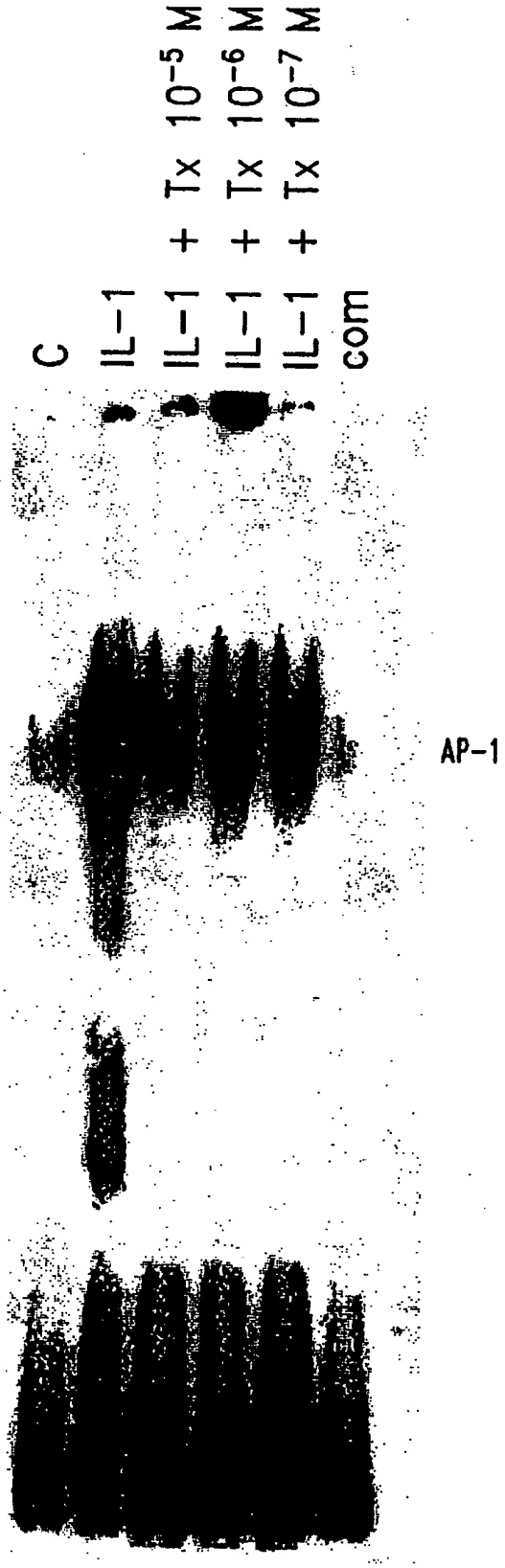


Fig. 11B

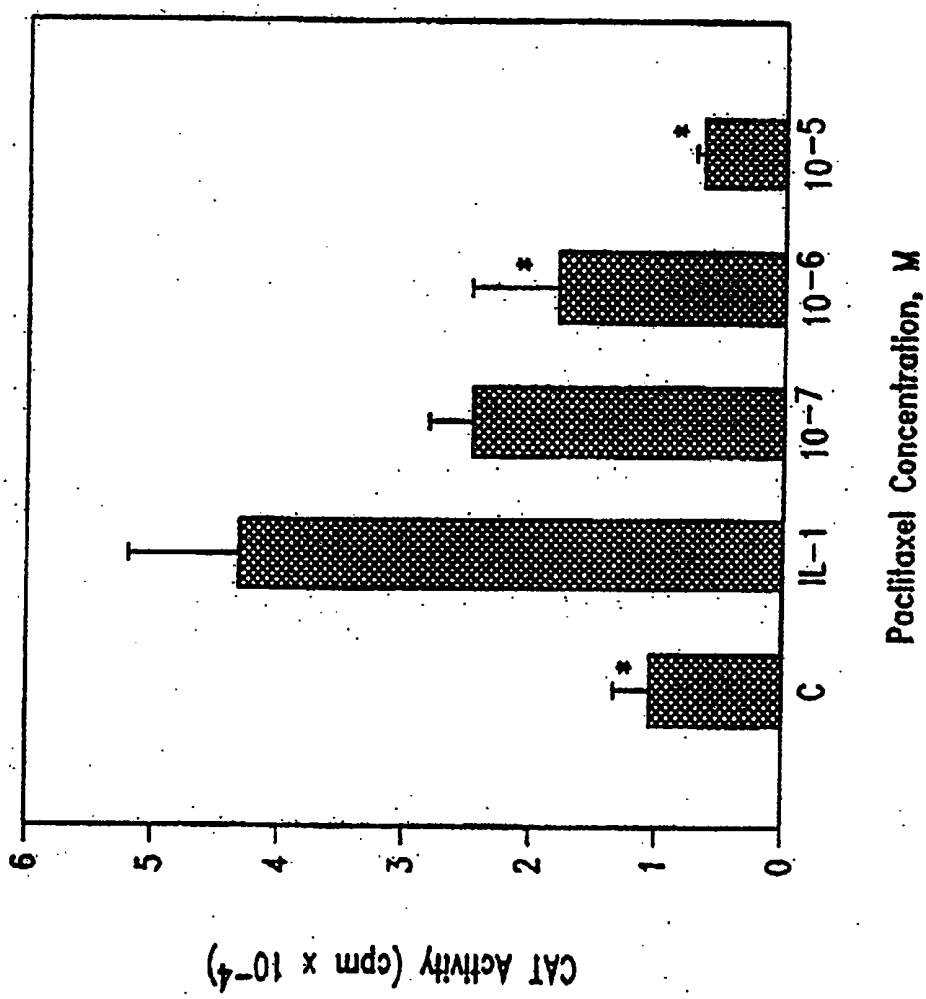

CAT Activity (cpm x 10^-4)
0
1
2
3
4
5
6
C
IL-1
10-7
10-6
10-5
Paclitaxel Concentration, M
*
*
*

Fig. 11C

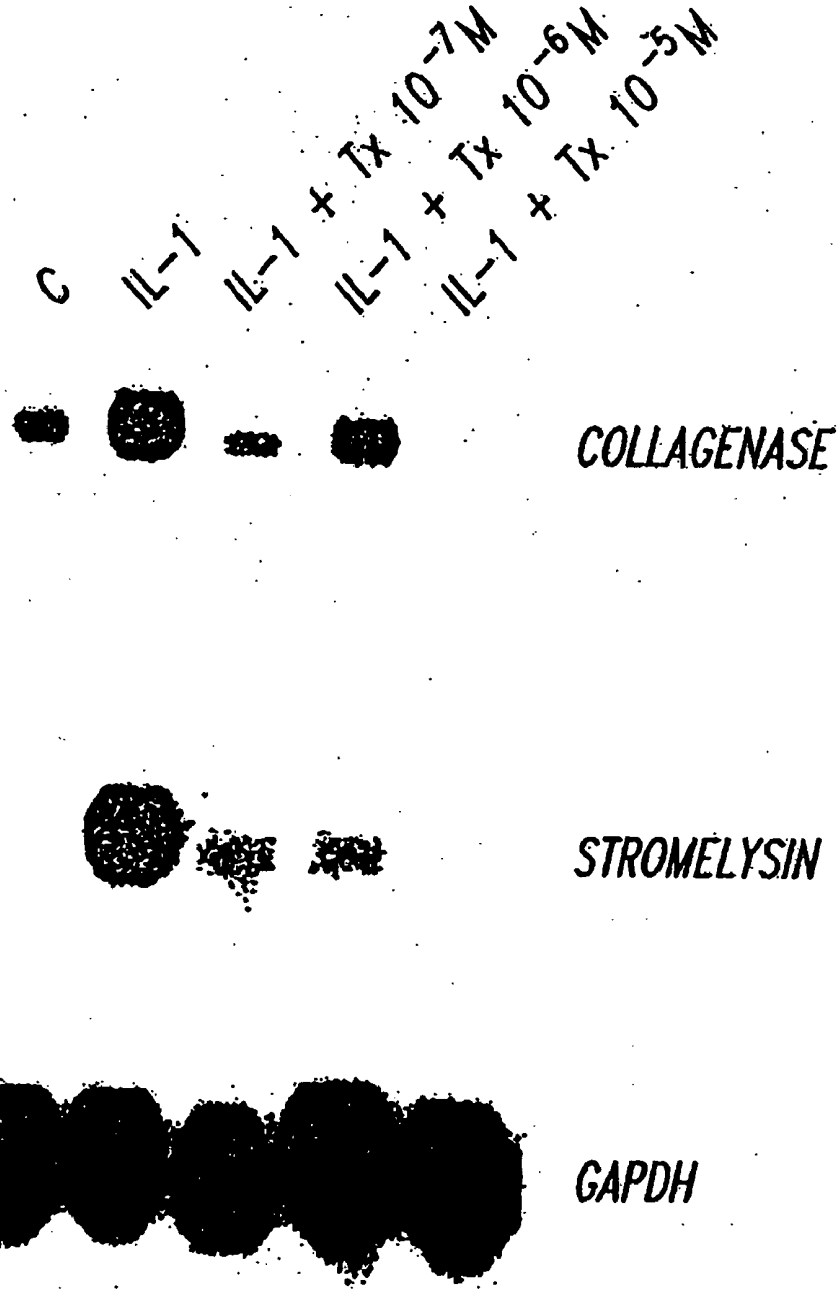

C
IL-1
IL-1 + Tx 10-7M
IL-1 + Tx 10-6M
IL-1 + Tx 10-5M
COLLAGENASE
STROMELYSIN
GAPDH

Fig. 11D

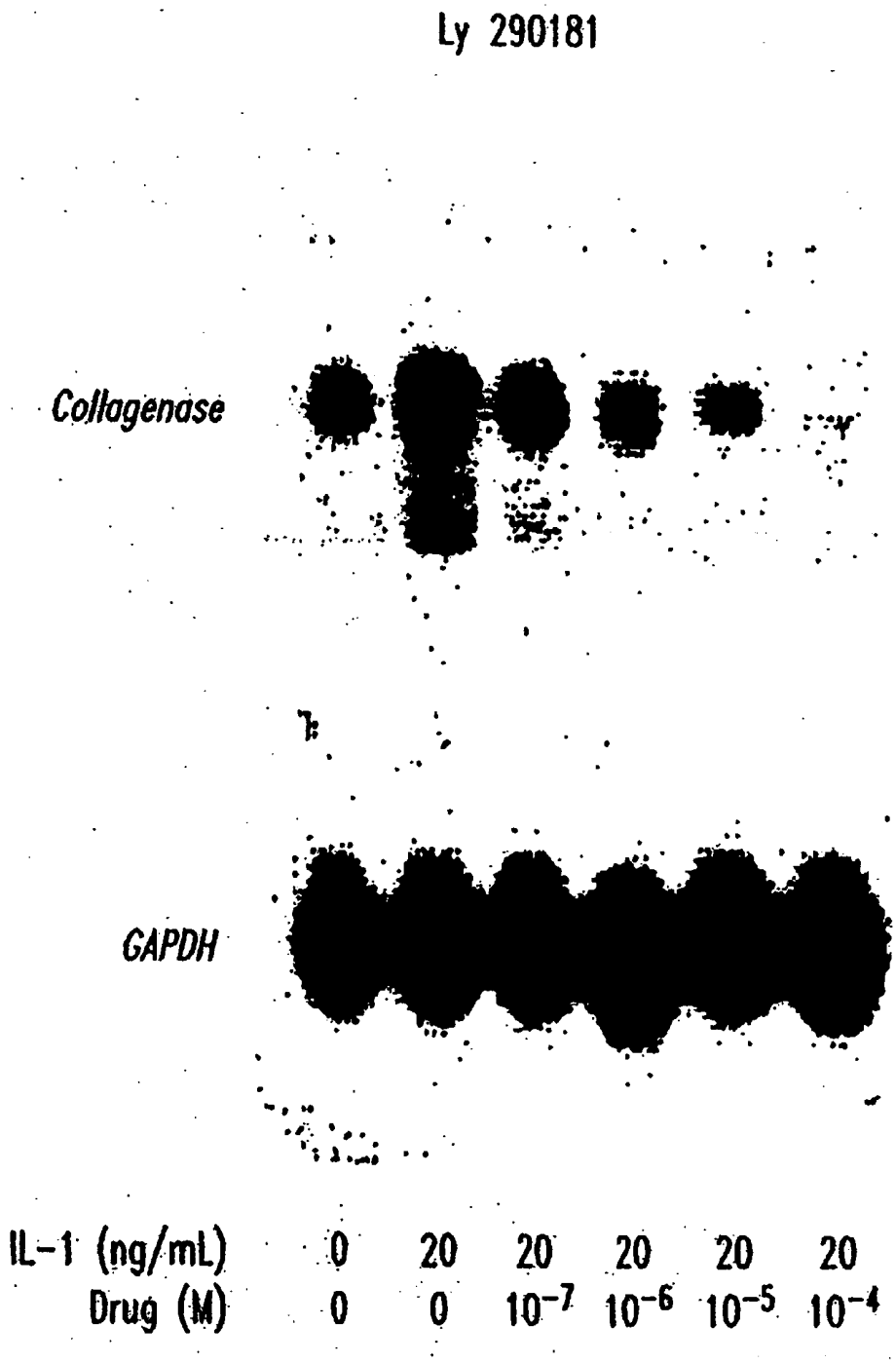

Ly 290181
Collagenase
GAPDH
IL-1 (ng/mL) 0 20 20 20 20 20
Drug (M) 0 0 10^{-7} 10^{-6} 10^{-5} 10^{-4}

Fig. 12A

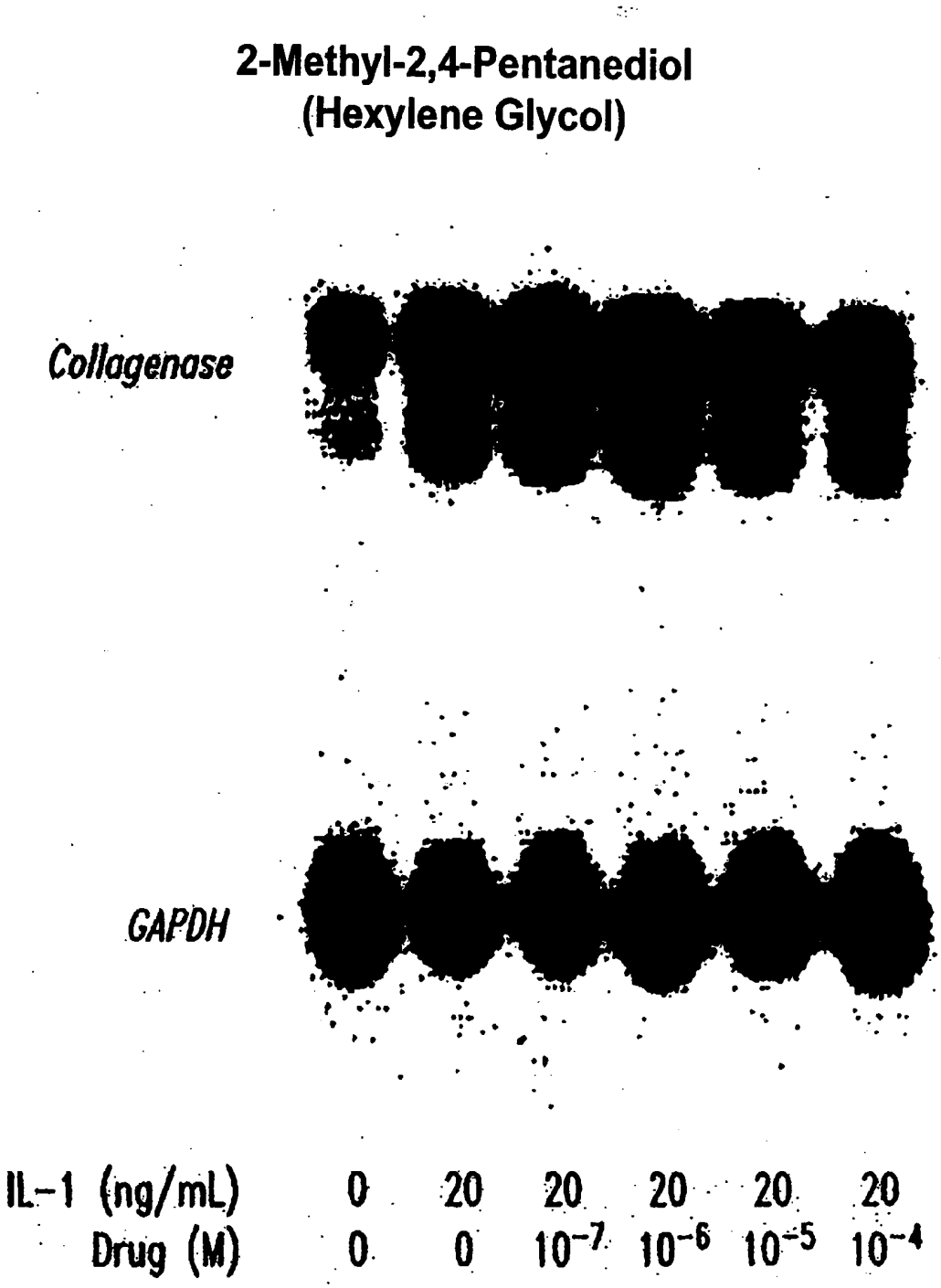

2-Methyl-2,4-Pentanediol
(Hexylene Glycol)
Collagenase
GAPDH
IL-1 (ng/mL) 0 20 20 20 20 20
Drug (M) 0 0 10^{-7} 10^{-6} 10^{-5} 10^{-4}

Fig. 12B

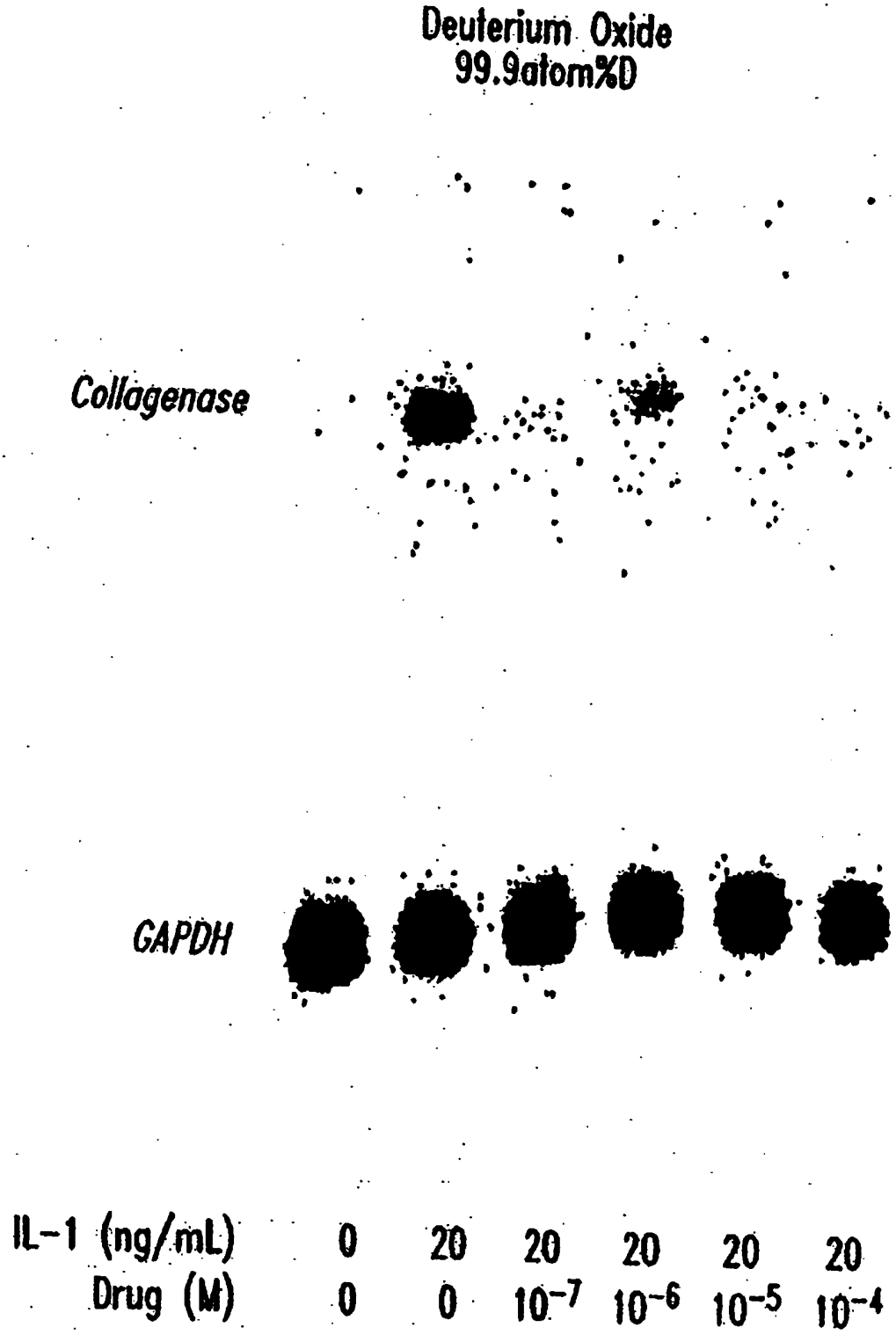

Deuterium Oxide
99.9atom%D
Collagenase
GAPDH
IL-1 (ng/mL) 0 20 20 20 20 20
Drug (M) 0 0 10-7 10-6 10-5 10-4

Fig. 12C

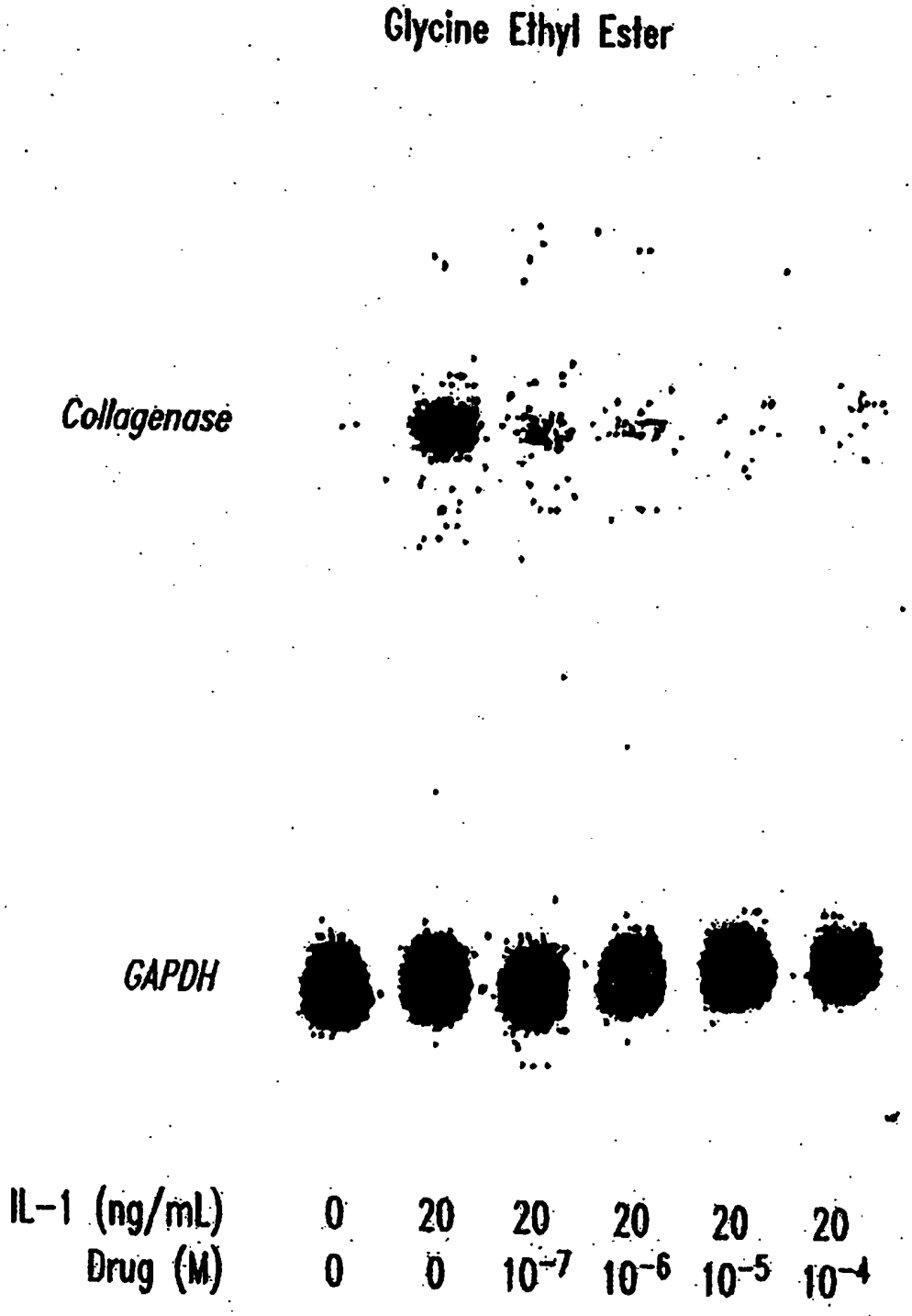

Glycine Ethyl Ester
Collagenase
GAPDH
IL-1 (ng/mL) 0 20 20 20 20 20
Drug (M) 0 0 10^{-7} 10^{-6} 10^{-5} 10^{-4}

Fig. 12D

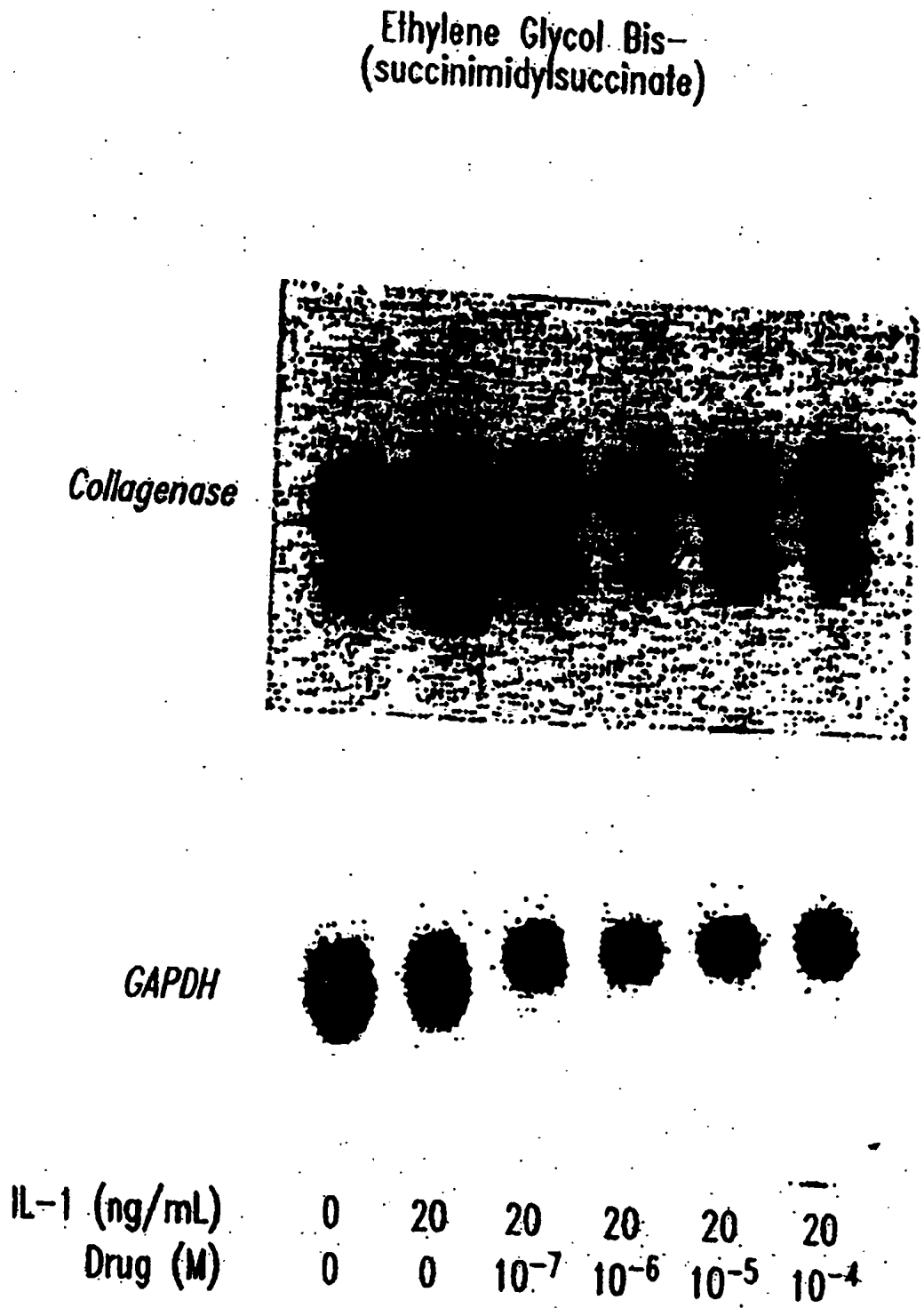

Ethylene Glycol Bis-
(succinimidylsuccinate)
Collagenase
GAPDH
IL-1 (ng/mL) 0 20 20 20 20 20
Drug (M) 0 0 10^{-7} 10^{-6} 10^{-5} 10^{-4}

Fig. 12E

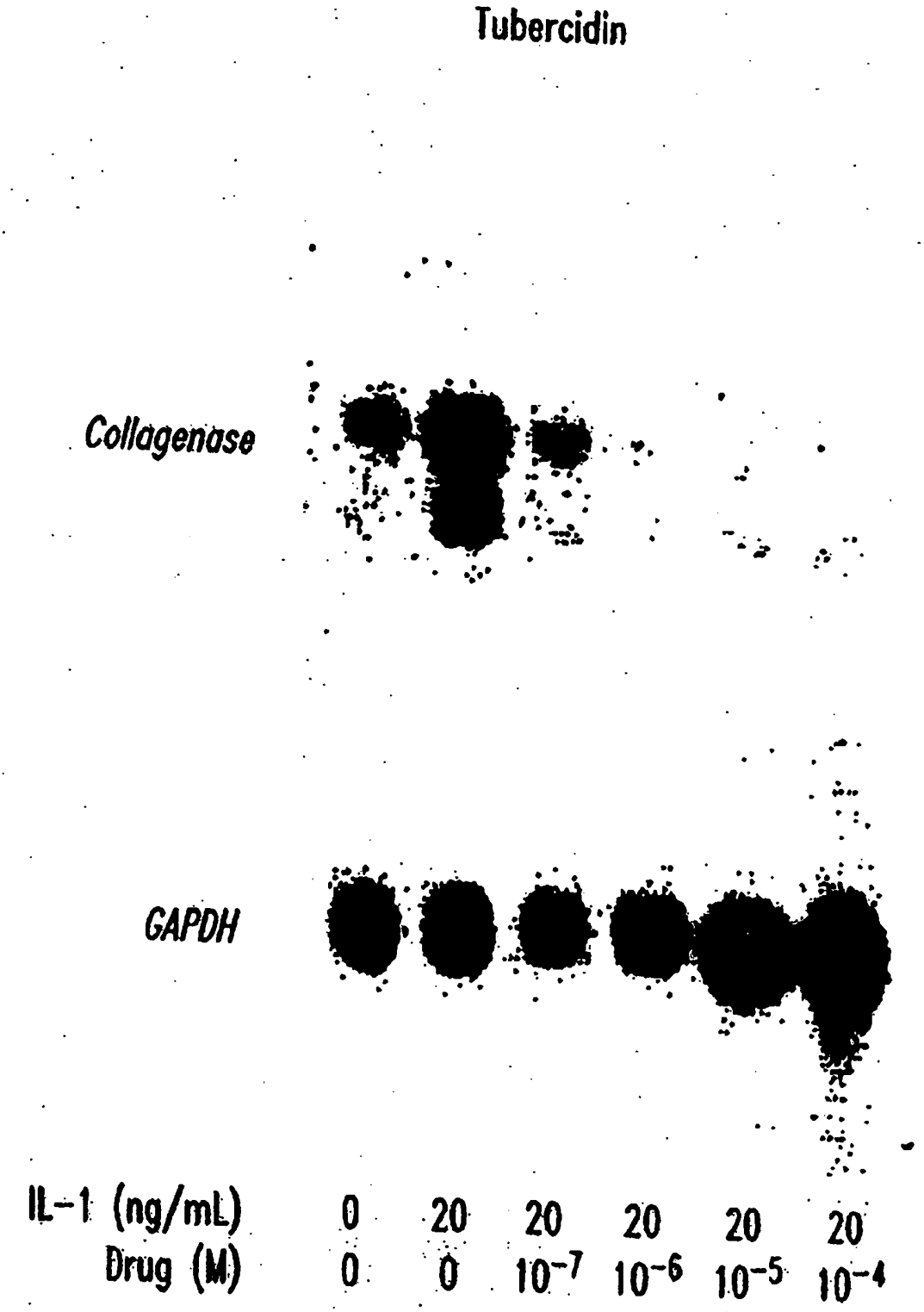

Tubercidin
Collagenase
GAPDH
IL-1 (ng/mL) 0 20 20 20 20 20
Drug (M) 0 0 10^{-7} 10^{-6} 10^{-5} 10^{-4}

Fig. 12F

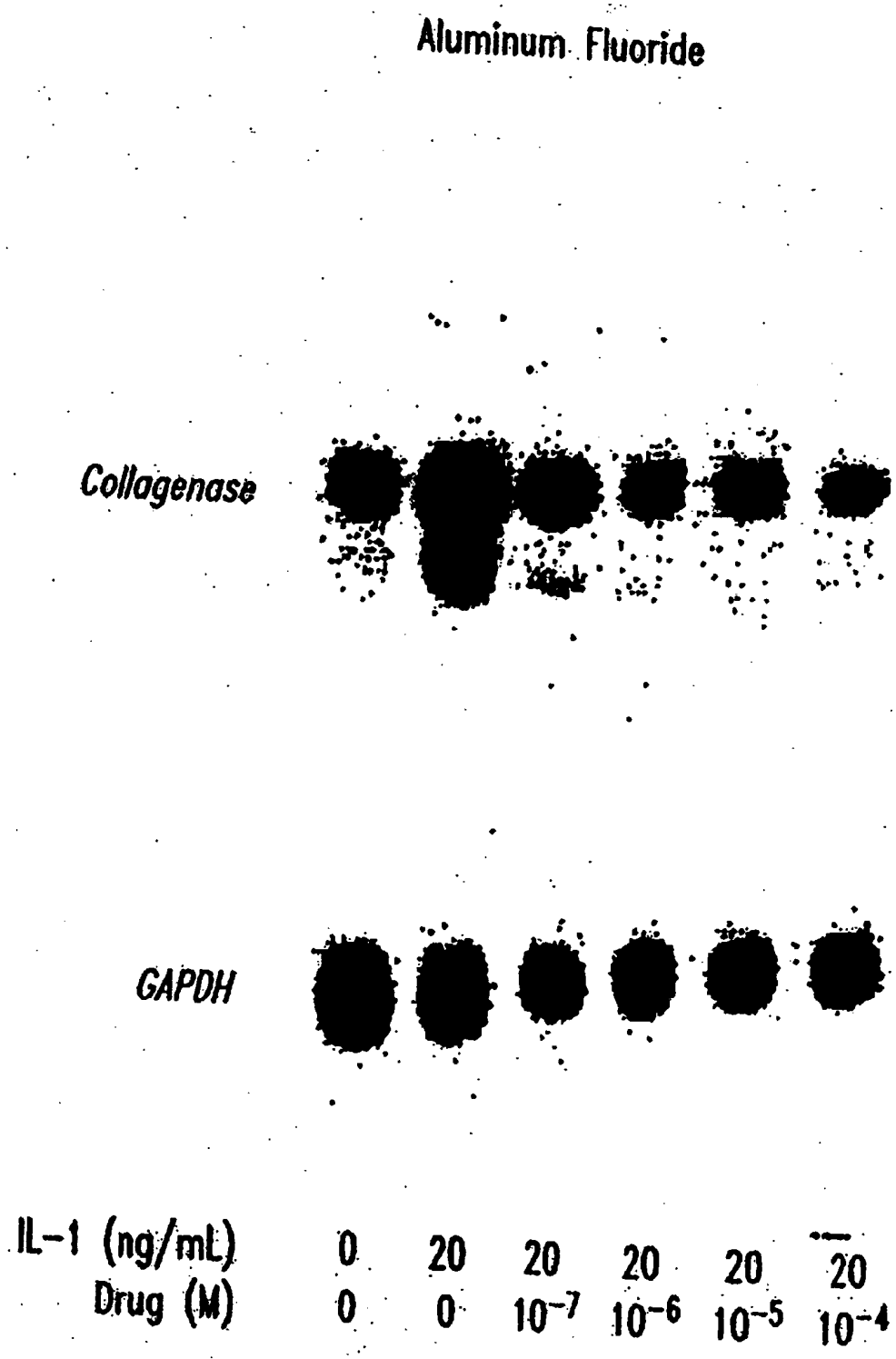

Aluminum Fluoride
Collagenase
GAPDH
IL-1 (ng/mL) 0 20 20 20 20 20
Drug (M) 0 0 10^{-7} 10^{-6} 10^{-5} 10^{-4}

Fig. 12G

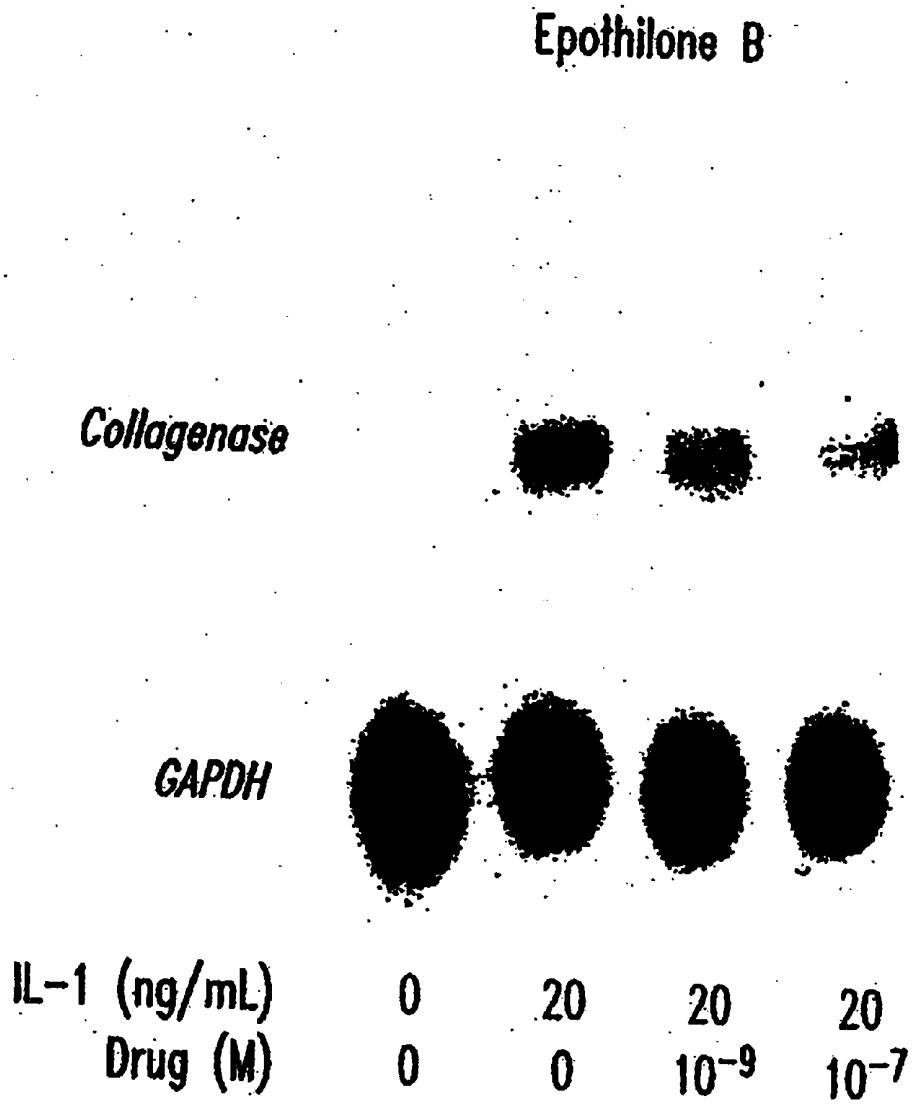

Epothilone B
Collagenase
GAPDH
IL-1 (ng/mL) 0 20 20 20
Drug (M) 0 0 10^{-9} 10^{-7}

Fig. 12H

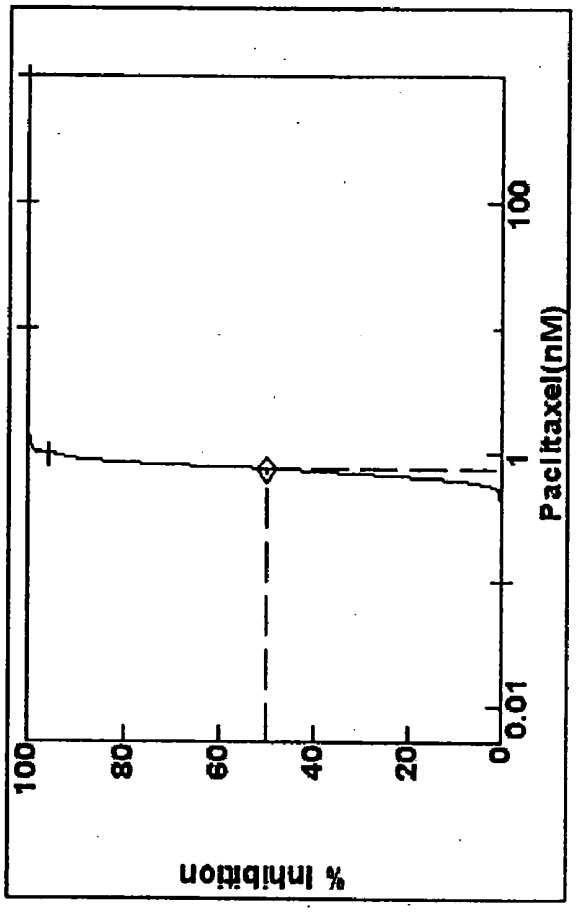


Fig. 13

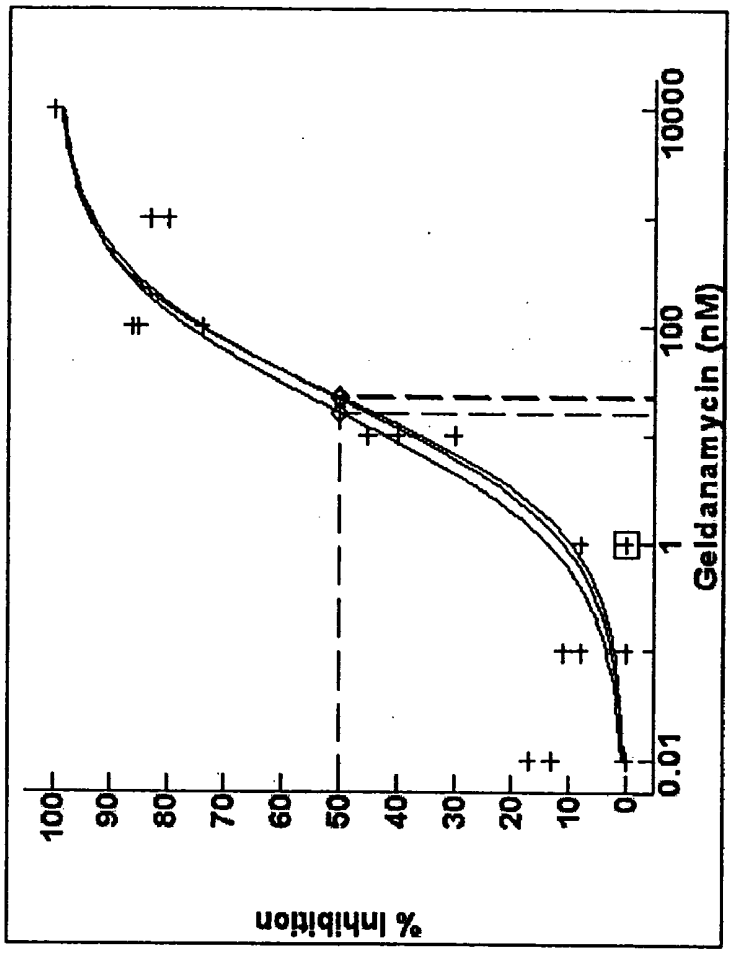

% Inhibition
100
90
80
70
60
50
40
30
20
10
0
0.01
1
100
10000
Geldanamycin (nM)

Fig. 14

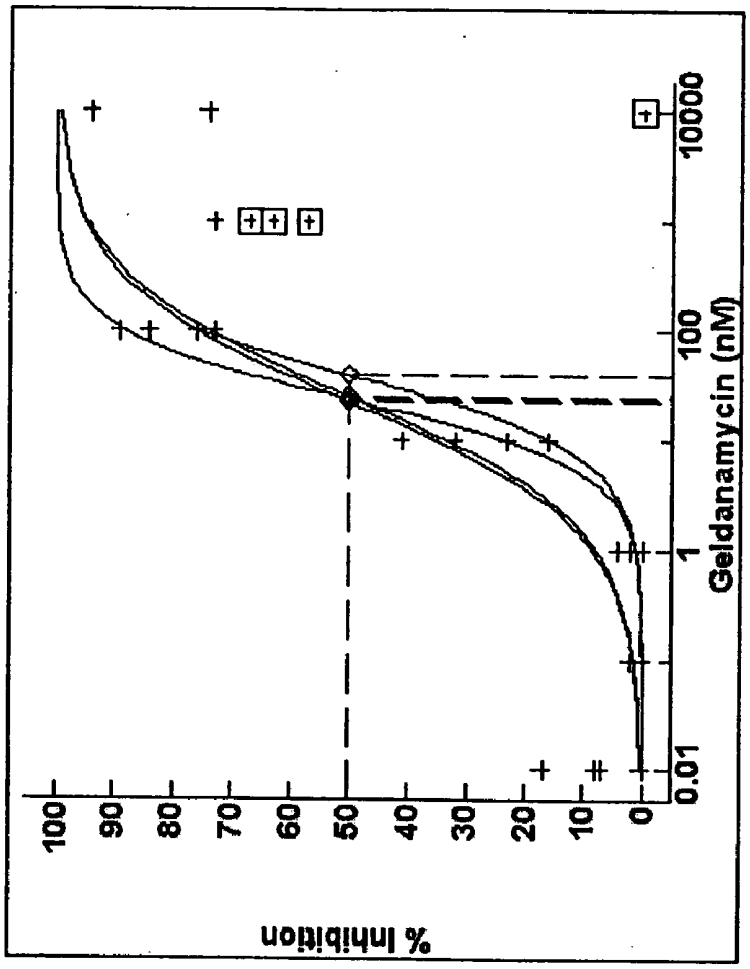

% Inhibition
100
90
80
70
60
50
40
30
20
10
0
Geldanamycin (nM)
10000
100
1
0.01

Fig. 15

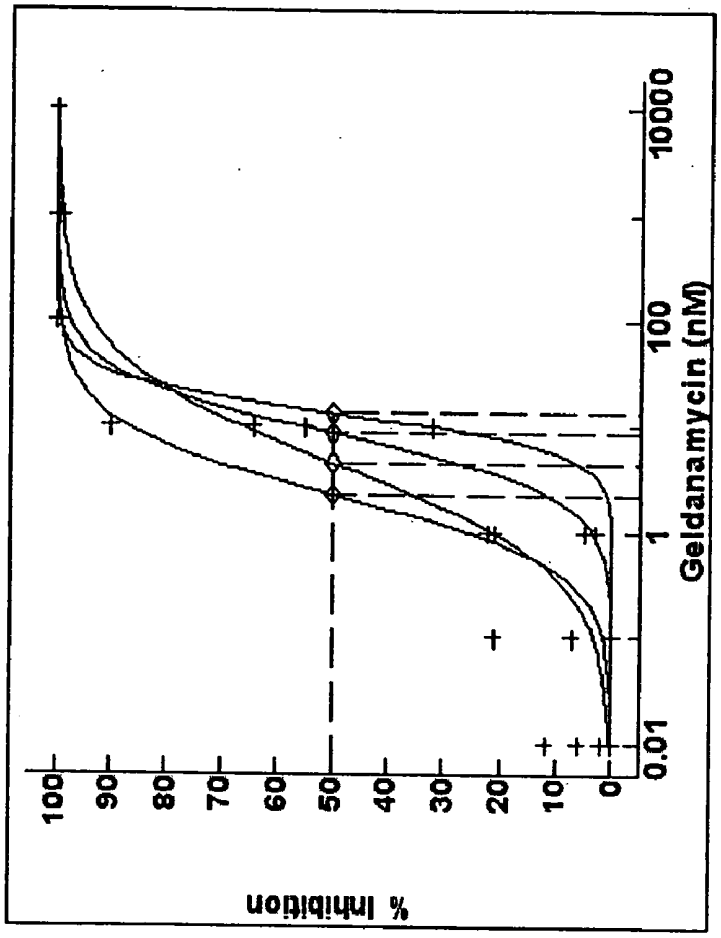
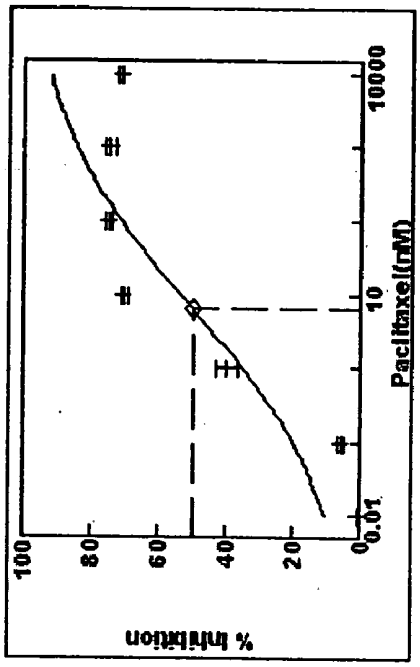
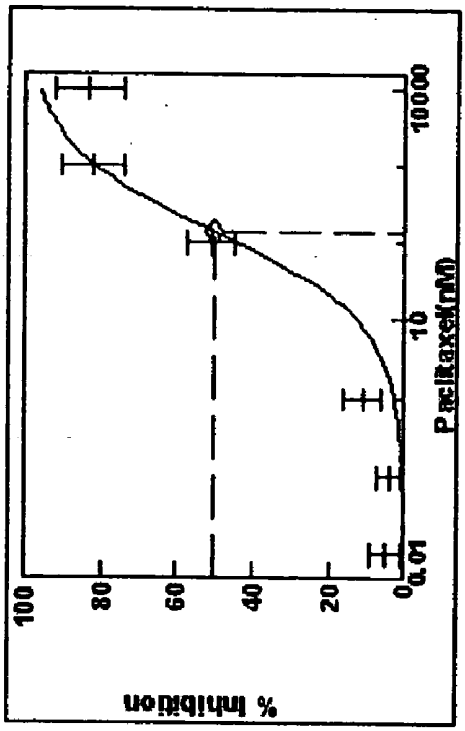

% Inhibition
100
90
80
70
60
50
40
30
20
10
0
0.01
1
100
10000
Geldanamycin (nM)

Fig. 16



Paclitaxel IC_{50}=7 nM for proliferation of human smooth muscle cells.

Fig. 17



Paclitaxel IC_{50}=134 nM for proliferation of the murine RAW 264.7 macrophage cell line.

Fig. 18

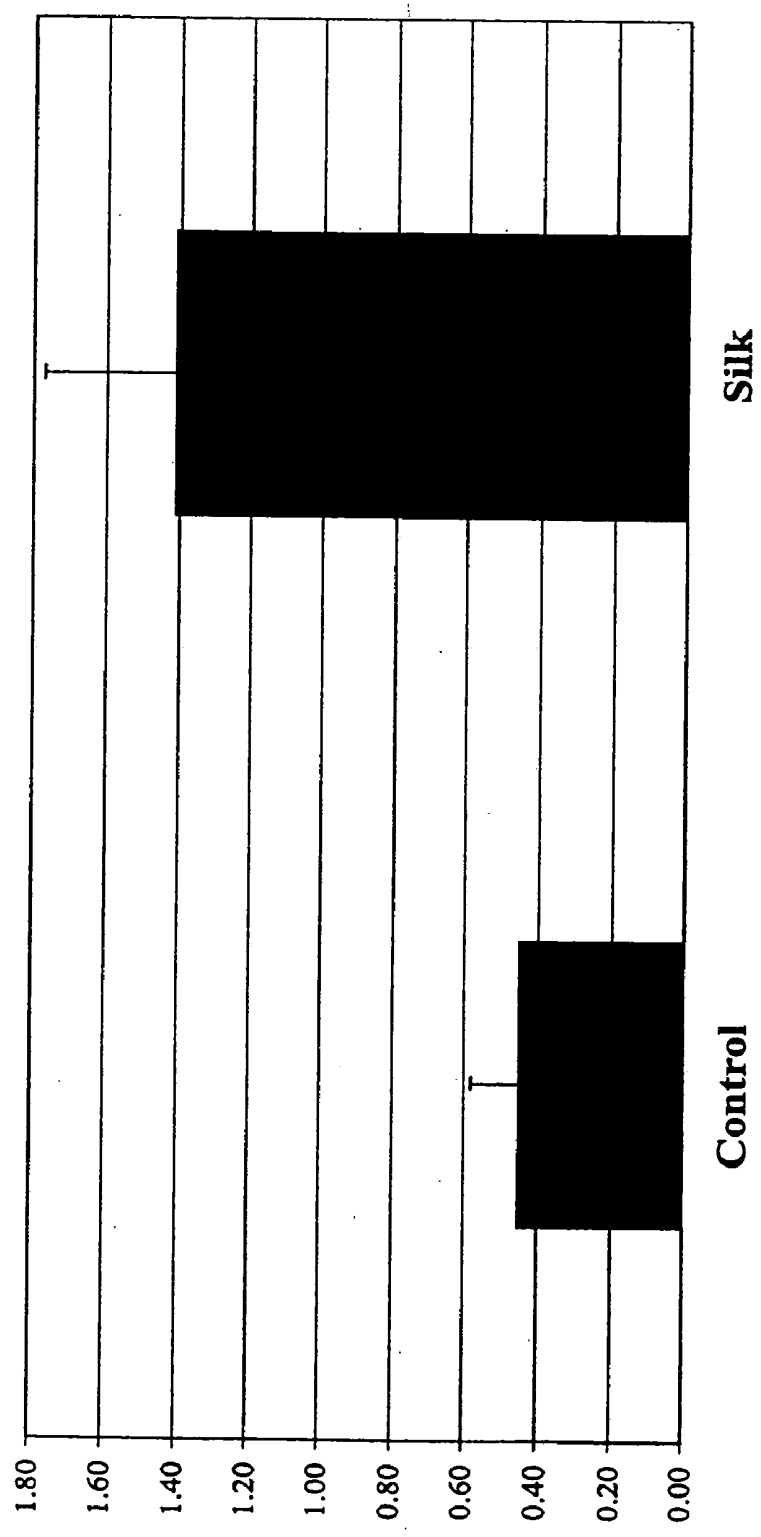


Fig. 19

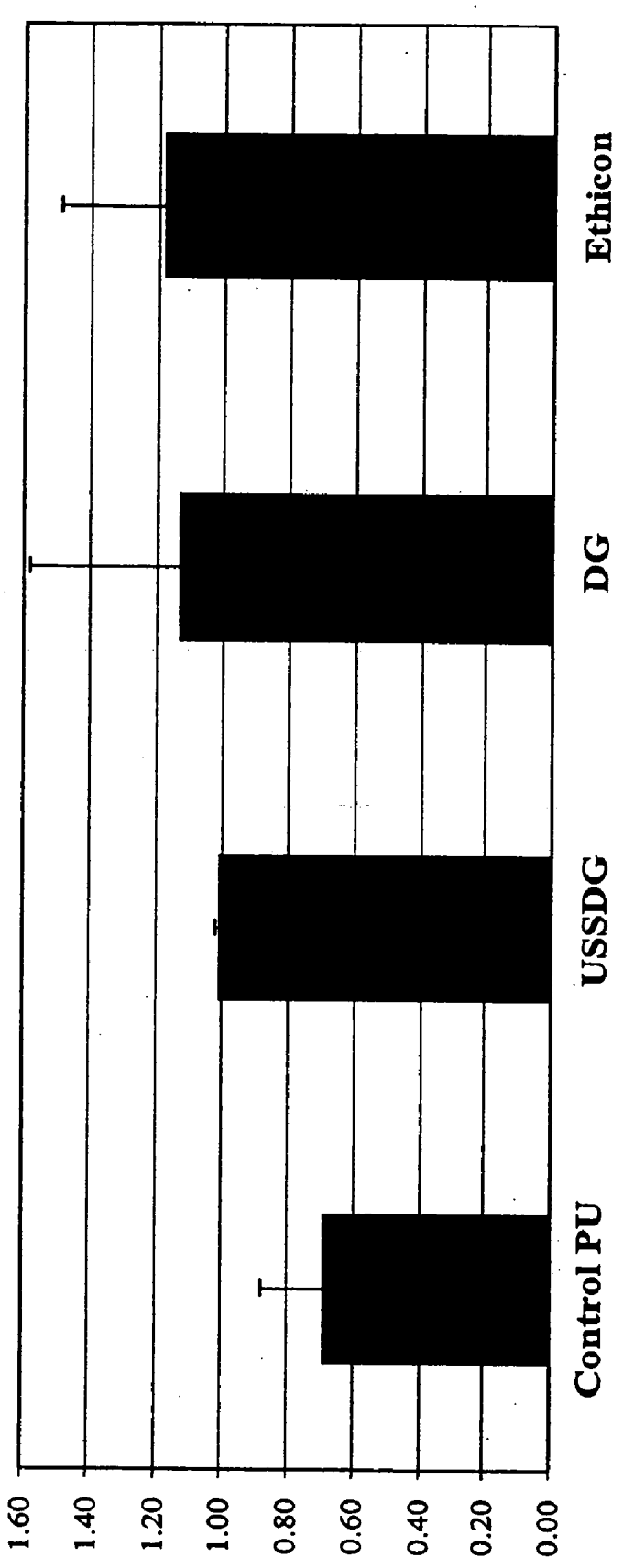

1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
Control PU
USSDG
DG
Ethicon

Fig. 20

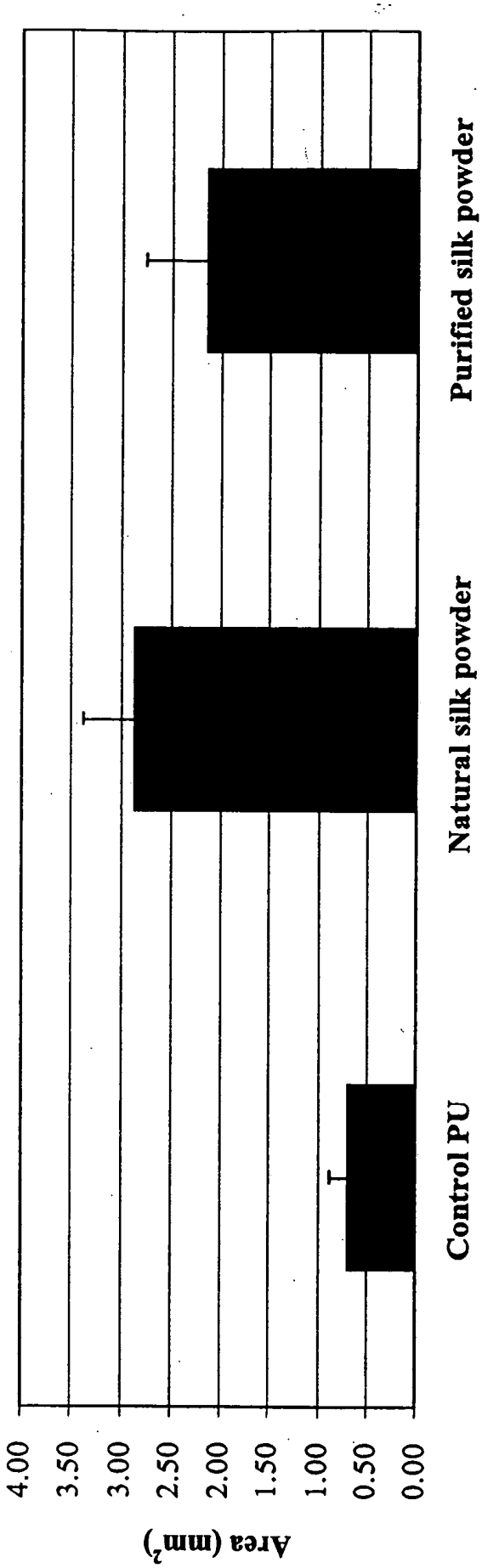

Area (mm²)
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
Control PU
Natural silk powder
Purified silk powder

Fig. 21

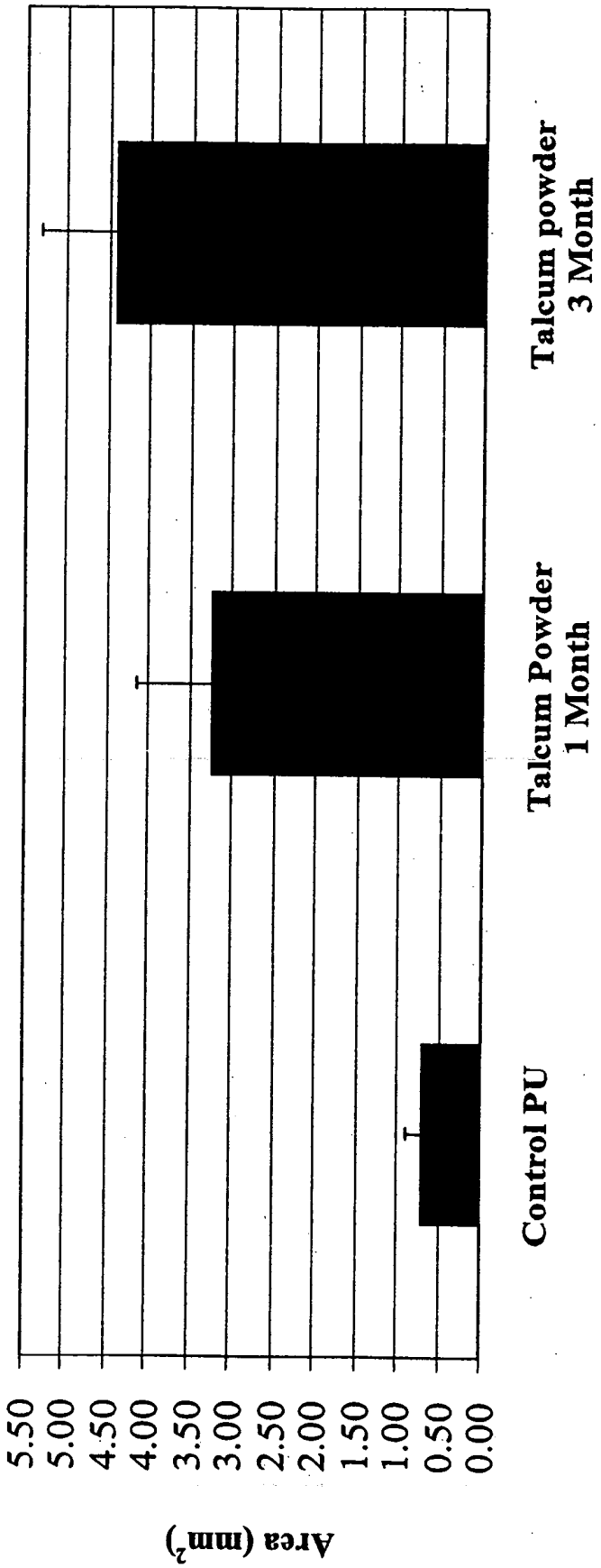

Area (mm²)
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
Control PU
Talcum Powder 1 Month
Talcum powder 3 Month

Fig. 22

ELECTRICAL DEVICES AND ANTI-SCARRING AGENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a Continuation of co-pending U.S. application Ser. No. 10/996,355, filed Nov. 22, 2004; which is a Continuation-in-Part of U.S. application Ser. Nos. 10/986,231, filed Nov. 10, 2004; and Ser. No. 10/986,230, filed Nov. 10, 2004; which application also claims the benefit under 35 U.S.C. 119(e) of U.S. Provisional Application Ser. Nos. 60/586,861, filed Jul. 9, 2004; 60/578,471, filed Jun. 9, 2004; 60/526,541, filed Dec. 3, 2003; 60/525,226, filed Nov. 24, 2003; 60/523,908, filed Nov. 20, 2003; and 60/524,023, filed Nov. 20, 2003, which applications are incorporated herein by reference in their entireties.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] The present invention relates generally to pharmaceutical compositions, methods and devices, and more specifically, to compositions and methods for preparing and using medical implants to make them resistant to overgrowth by inflammatory, fibrous and glial scar tissue.

[0004] 2. Description of the Related Art

[0005] Medical devices having electrical components, such as electrical pacing or stimulating devices, can be implanted in the body to provide electrical conduction to the central and peripheral nervous system (including the autonomic system), cardiac muscle tissue (including myocardial conduction pathways), smooth muscle tissue and skeletal muscle tissue. These electrical impulses are used to treat many bodily dysfunctions and disorders by blocking, masking, stimulating, or replacing electrical signals within the body. Examples include pacemaker leads used to maintain the normal rhythmic beating of the heart; defibrillator leads used to "re-start" the heart when it stops beating; peripheral nerve stimulating devices to treat chronic pain; deep brain electrical stimulation to treat conditions such as tremor, Parkinson's disease, movement disorders, epilepsy, depression and psychiatric disorders; and vagal nerve stimulation to treat epilepsy, depression, anxiety, obesity, migraine and Alzheimer's Disease.

[0006] The clinical function of an electrical device such as a cardiac pacemaker lead, neurostimulation lead, or other electrical lead depends upon the device being able to effectively maintain intimate anatomical contact with the target tissue (typically electrically excitable cells such as muscle or nerve) such that electrical conduction from the device to the tissue can occur. Unfortunately, in many instances when these devices are implanted in the body, they are subject to a "foreign body" response from the surrounding host tissues. The body recognizes the implanted device as foreign, which triggers an inflammatory response followed by encapsulation of the implant with fibrous connective tissue (or glial tissue—called "gliosis"—when it occurs within the central nervous system). Scarring (i.e., fibrosis or gliosis) can also result from trauma to the anatomical structures and tissue surrounding the implant during the implantation of the device. Lastly, fibrous encapsulation of the device can occur even after a successful implantation if the device is manipulated (some patients continuously "fiddle" with a subcutaneous implant) or irritated by the daily activities of the patient. When scarring occurs around the implanted device, the electrical characteristics of the electrode-tissue interface degrade, and the device may fail to function properly. For example, it may require additional electrical current from the lead to overcome the extra resistance imposed by the intervening scar (or glial) tissue. This can shorten the battery life of an implant (making more frequent removal and re-implantation necessary), prevent electrical conduction altogether (rendering the implant clinically ineffective) and/or cause damage to the target tissue. Additionally, the surrounding tissue may be inadvertently damaged from the inflammatory foreign body response, which can result in loss of function or tissue necrosis.

BRIEF SUMMARY OF THE INVENTION

[0007] Briefly stated, the present invention discloses pharmaceutical agents which inhibit one or more aspects of the production of excessive fibrous (scar) or glial tissue. In one aspect, the present invention provides compositions for delivery of selected therapeutic agents via medical implants or implantable electrical medical devices, as well as methods for making and using these implants and devices. Compositions and methods are described for coating electrical medical devices and implants with drug-delivery compositions such that the pharmaceutical agent is delivered in therapeutic levels over a period sufficient to prevent the device electrode from being encapsulated in fibrous or glial tissue and to allow normal electrical conduction to occur. Alternatively, locally administered compositions (e.g., topicals, injectables, liquids, gels, sprays, microspheres, pastes, wafers) containing an inhibitor of fibrosis (or gliosis) are described that can be applied to the tissue adjacent to the electrical medical device or implant, such that the pharmaceutical agent is delivered in therapeutic levels over a period sufficient to prevent the device electrode from being encapsulated in fibrous or glial tissue. And finally, numerous specific cardiac and neurological implants and devices are described that produce superior clinical results as a result of being coated with agents that reduce excessive scarring and fibrous (or glial) tissue accumulation as well as other related advantages.

[0008] Within one aspect of the invention, drug-coated or drug-impregnated implants and medical devices are provided which reduce fibrosis or gliosis in the tissue surrounding the electrical device or implant, or inhibit scar development on the device/implant surface (particularly the electrical lead), thus enhancing the efficacy of the procedure. For example, it may require additional electrical current from the lead to overcome the extra resistance imposed by the intervening scar (or glial) tissue. This can shorten the battery life of an implant (making more frequent removal and re-implantation necessary), prevent electrical conduction altogether (rendering the implant clinically ineffective) and/or cause damage to the target tissue. Within various embodiments, fibrosis or gliosis is inhibited by local or systemic release of specific pharmacological agents that become localized to the adjacent tissue.

[0009] The repair of tissues following a mechanical or surgical intervention, such as the implantation of an electrical device, involves two distinct processes: (1) regeneration (the replacement of injured cells by cells of the same type

and (2) fibrosis (the replacement of injured cells by connective tissue). There are four general components to the process of fibrosis (or scarring) including: formation of new blood vessels (angiogenesis), migration and proliferation of connective tissue cells (such as fibroblasts or smooth muscle cells), deposition of extracellular matrix (ECM), and remodeling (maturation and organization of the fibrous tissue). As utilized herein, "inhibits (reduces) fibrosis" should be understood to refer to agents or compositions which decrease or limit the formation of fibrous tissue (i.e., by reducing or inhibiting one or more of the processes of angiogenesis, connective tissue cell migration or proliferation, ECM production, and/or remodeling). In addition, numerous therapeutic agents described in this invention may have the additional benefit of also reducing tissue regeneration where appropriate.

[0010] It should be noted that in implantation procedures that cause injuries to the central nervous system (CNS), fibrosis is replaced by a process called gliosis (the replacement of injured or dead cells with glial tissue). Glial cells form the supporting tissue of the CNS and are comprised of macroglia (astrocytes, oligodendrocytes, ependyma cells) and microglia cells. Of these cell types, astrocytes are the principle cells responsible for repair and scar formation in the brain and spinal cord. Gliosis is the most important indicator of CNS damage and consists of astrocyte hypertrophy (increase in size) and hyperplasia (increase in cell number as a result of cell division) in response to injury or trauma, such as that caused by the implantation of a medical device. Astrocytes are responsible for phagocytosing dead or damaged tissue and repairing the injury with glial tissue and thus, serve a similar role to that performed by fibroblasts in scarring outside the brain. In medical devices implanted into the CNS, it is the hypertrophy and proliferation of astrocytes (gliosis) that leads to the formation of a "scar-like" capsule around the implant which can interfere with electrical conduction from the device to the neuronal tissue.

[0011] Within certain embodiments of the invention, an implant or device is adapted to release an agent that inhibits fibrosis or gliosis through one or more of the mechanisms sited herein. Within certain other embodiments of the invention, an implant or device contains an agent that while remaining associated with the implant or device, inhibits fibrosis between the implant or device and the tissue where the implant or device is placed by direct contact between the agent and the tissue surrounding the implant or device.

[0012] Within related aspects of the present invention, cardiac and neurostimulation devices are provided comprising an implant or device, wherein the implant or device releases an agent which inhibits fibrosis (or gliosis) in vivo. "Release of an agent" refers to any statistically significant presence of the agent, or a subcomponent thereof, which has disassociated from the implant/device and/or remains active on the surface of (or within) the device/implant. Within yet other aspects of the present invention, methods are provided for manufacturing a medical device or implant, comprising the step of coating (e.g., spraying, dipping, wrapping, or administering drug through) a medical device or implant. Additionally, the implant or medical device can be constructed so that the device itself is comprised of materials which inhibit fibrosis in or around the implant. A wide variety of electrical medical devices and implants may be utilized within the context of the present invention, depending on the site and nature of treatment desired.

[0013] Within various embodiments of the invention, the implant or device is further coated with a composition or compound, which delays the onset of activity of the fibrosis-inhibiting (or gliosis-inhibiting) agent for a period of time after implantation. Representative examples of such agents include heparin, PLGA/MePEG, PLA, and polyethylene glycol. Within further embodiments, the fibrosis-inhibiting (or gliosis-inhibiting) implant or device is activated before, during, or after deployment (e.g., an inactive agent on the device is first activated to one that reduces or inhibits an in vivo fibrotic or gliotic reaction).

[0014] Within various embodiments of the invention, the tissue surrounding the implant or device is treated with a composition or compound that contains an inhibitor of fibrosis or gliosis. Locally administered compositions (e.g., topicals, injectables, liquids, gels, sprays, microspheres, pastes, wafers) or compounds containing an inhibitor of fibrosis (or gliosis) are described that can be applied to the surface of, or infiltrated into, the tissue adjacent to the electrical medical device or implant, such that the pharmaceutical agent is delivered in therapeutic levels over a period sufficient to prevent the device electrode from being encapsulated in fibrous or glial tissue. This can be done in lieu of coating the device or implant with a fibrosis/gliosis-inhibitor, or done in addition to coating the device or implant with a fibrosis/gliosis-inhibitor. The local administration of the fibrosis/gliosis-inhibiting agent can occur prior to, during, or after implantation of the electrical device itself.

[0015] Within various embodiments of the invention, an electrical device or implant is coated on one aspect, portion or surface with a composition which inhibits fibrosis, as well as being coated with a composition or compound which promotes scarring on another aspect, portion or surface of the device (i.e., to affix the body of the device into a particular anatomical space). Representative examples of agents that promote fibrosis and scarring include silk, silica, crystalline silicates, bleomycin, quartz dust, neomycin, talc, metallic beryllium and oxides thereof, retinoic acid compounds, copper, leptin, growth factors, a component of extracellular matrix; fibronectin, collagen, fibrin, or fibrinogen, polylysine, poly(ethylene-co-vinylacetate), chitosan, N-carboxybutylchitosan, and RGD proteins; vinyl chloride or a polymer of vinyl chloride; an adhesive selected from the group consisting of cyanoacrylates and crosslinked poly-(ethylene glycol)—methylated collagen; an inflammatory cytokine (e.g., TGFβ, PDGF, VEGF, bFGF, TNFα, NGF, GM-CSF, IGF-1, IL-1, IL-1-β, IL-8, IL-6, and growth hormone); connective tissue growth factor (CTGF) as well as analogues and derivatives thereof.

[0016] Also provided by the present invention are methods for treating patients undergoing surgical, endoscopic or minimally invasive therapies where an electrical device or implant is placed as part of the procedure. As utilized herein, it should be understood that "inhibits fibrosis or gliosis" refers to a statistically significant decrease in the amount of scar tissue in or around the device or an improvement in the interface between the electrical device or implant and the tissue, which may or may not lead to a permanent prohibition of any complications or failures of the device/implant.

[0017] The pharmaceutical agents and compositions are utilized to create novel drug-coated implants and medical

devices that reduce the foreign body response to implantation and limit the growth of reactive tissue on the surface of, or around in the tissue surrounding the device, such that performance is enhanced. Electrical medical devices and implants coated with selected pharmaceutical agents designed to prevent scar tissue overgrowth and improve electrical conduction can offer significant clinical advantages over uncoated devices.

[0018] For example, in one aspect the present invention is directed to electrical stimulatory devices that comprise a medical implant and at least one of (i) an anti-scarring agent and (ii) a composition that comprises an anti-scarring agent. The agent is present so as to inhibit scarring that may otherwise occur when the implant is placed within an animal. In another aspect the present invention is directed to methods wherein both an implant and at least one of (i) an anti-scarring agent and (ii) a composition that comprises an anti-scarring agent, are placed into an animal, and the agent inhibits scarring that may otherwise occur. These and other aspects of the invention are summarized below.

[0019] Thus, in various independent aspects, the present invention provides a device, comprising a cardiac or neurostimulator implant and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring. These and other devices are described in more detail herein.

[0020] In each of the aforementioned devices, in separate aspects, the present invention provides that: the agent is a cell cycle inhibitor; the agent is an anthracycline; the agent is a taxane; the agent is a podophyllotoxin; the agent is an immunomodulator; the agent is a heat shock protein 90 antagonist; the agent is a HMGCoA reductase inhibitor; the agent is an inosine monophosphate dehydrogenase inhibitor; the agent is an NF kappa B inhibitor; the agent is a P38 MAP kinase inhibitor. These and other agents are described in more detail herein.

[0021] In additional aspects, for each of the aforementioned devices combined with each of the aforementioned agents, it is, for each combination, independently disclosed that the agent may be present in a composition along with a polymer. In one embodiment of this aspect, the polymer is biodegradable. In another embodiment of this aspect, the polymer is non-biodegradable. Other features and characteristics of the polymer, which may serve to describe the present invention for every combination of device and agent described above, are set forth in greater detail herein.

[0022] In addition to devices, the present invention also provides methods. For example, in additional aspects of the present invention, for each of the aforementioned devices, and for each of the aforementioned combinations of the devices with the anti-scarring (or anti-gliotic) agents, the present invention provides methods whereby a specified device is implanted into an animal, and a specified agent associated with the device inhibits scarring (or gliosis) that may otherwise occur. Each of the devices identified herein may be a "specified device", and each of the anti-scarring agents identified herein may be an "anti-scarring agent", where the present invention provides, in independent embodiments, for each possible combination of the device and the agent.

[0023] The agent may be associated with the device prior to the device being placed within the animal. For example, the agent (or composition comprising the agent) may be coated onto an implant, and the resulting device then placed within the animal. In addition, or alternatively, the agent may be independently placed within the animal in the vicinity of where the device is to be, or is being, placed within the animal. For example, the agent may be sprayed or otherwise placed onto, adjacent to, and/or within the tissue that will be contacting the medical implant or may otherwise undergo scarring. To this end, the present invention provides placing a cardiac or neurostimulation implant and an anti-scarring (or anti-gliosis) agent or a composition comprising an anti-scarring (or anti-gliosis) agent into an animal host, wherein the agent inhibits scarring or gliosis.

[0024] In each of the aforementioned methods, in separate aspects, the present invention provides that: the agent is a cell cycle inhibitor; the agent is an anthracycline; the agent is a taxane; the agent is a podophyllotoxin; the agent is an immunomodulator; the agent is a heat shock protein 90 antagonist; the agent is a HMGCoA reductase inhibitor; the agent is an inosine monophosphate dehydrogenase inhibitor; the agent is an NF kappa B inhibitor; the agent is a P38 MAP kinase inhibitor. These and other agents which can inhibit fibrosis and gliosis are described in more detail herein.

[0025] In additional aspects, for each of the aforementioned methods used in combination with each of the aforementioned agents, it is, for each combination, independently disclosed that the agent may be present in a composition along with a polymer. In one embodiment of this aspect, the polymer is biodegradable. In another embodiment of this aspect, the polymer is non-biodegradable. Other features and characteristics of the polymer, which may serve to describe the present invention for every combination of device and agent described above, are set forth in greater detail herein.

[0026] These and other aspects of the present invention will become evident upon reference to the following detailed description and attached drawings. In addition, various references are set forth herein which describe in more detail certain procedures and/or compositions (e.g., polymers), and are therefore incorporated by reference in their entirety.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] **FIG. 1** is a diagram showing how a cell cycle inhibitor acts at one or more of the steps in the biological pathway.

[0028] **FIG. 2** is a graph showing the results for the screening assay for assessing the effect of mitoxantrone on nitric oxide production by THP-1 macrophages.

[0029] **FIG. 3** is a graph showing the results for the screening assay for assessing the effect of Bay 11-7082 on TNF-alpha production by THP-1 macrophages.

[0030] **FIG. 4** is a graph showing the results for the screening assay for assessing the effect of rapamycin concentration for TNFα production by THP-1 macrophages.

[0031] **FIG. 5** is graph showing the results of a screening assay for assessing the effect of mitoxantrone on proliferation of human fibroblasts.

[0032] **FIG. 6** is graph showing the results of a screening assay for assessing the effect of rapamycin on proliferation of human fibroblasts.

[0033] **FIG. 7** is graph showing the results of a screening assay for assessing the effect of paclitaxel on proliferation of human fibroblasts.

[0034] **FIG. 8** is a picture that shows an uninjured carotid artery from a rat balloon injury model.

[0035] **FIG. 9** is a picture that shows an injured carotid artery from a rat balloon injury model.

[0036] **FIG. 10** is a picture that shows a paclitaxel/mesh treated carotid artery in a rat balloon injury model.

[0037] **FIG. 11A** schematically depicts the transcriptional regulation of matrix metalloproteinases.

[0038] **FIG. 11B** is a blot which demonstrates that IL-1 stimulates AP-1 transcriptional activity.

[0039] **FIG. 11C** is a graph which shows that IL-1 induced binding activity decreased in lysates from chondrocytes which were pretreated with paclitaxel.

[0040] **FIG. 11D** is a blot which shows that IL-1 induction increases collagenase and stromelysin in RNA levels in chondrocytes, and that this induction can be inhibited by pretreatment with paclitaxel.

[0041] FIGS. **12A-H** are blots that show the effect of various anti-microtubule agents in inhibiting collagenase expression.

[0042] **FIG. 13** is a graph showing the results of a screening assay for assessing the effect of paclitaxel on smooth muscle cell migration.

[0043] **FIG. 14** is a graph showing the results of a screening assay for assessing the effect of geldanamycin on IL-1β production by THP-1 macrophages.

[0044] **FIG. 15** is a graph showing the results of a screening assay for assessing the effect of geldanamycin on IL-8 production by THP-1 macrophages.

[0045] **FIG. 16** is a graph showing the results of a screening assay for assessing the effect of geldanamycin on MCP-1 production by THP-1 macrophages.

[0046] **FIG. 17** is graph showing the results of a screening assay for assessing the effect of paclitaxel on proliferation of smooth muscle cells.

[0047] **FIG. 18** is graph showing the results of a screening assay for assessing the effect of paclitaxel for proliferation of the murine RAW 264.7 macrophage cell line.

[0048] **FIG. 19** is a bar graph showing the area of granulation tissue in carotid arteries exposed to silk coated perivascular polyurethane (PU) films relative to arteries exposed to uncoated PU films.

[0049] **FIG. 20** is a bar graph showing the area of granulation tissue in carotid arteries exposed to silk suture coated perivascular PU films relative to arteries exposed to uncoated PU films.

[0050] **FIG. 21** is a bar graph showing the area of granulation tissue in carotid arteries exposed to natural and purified silk powder and wrapped with perivascular PU film relative to a control group in which arteries are wrapped with perivascular PU film only.

[0051] **FIG. 22** is a bar graph showing the area of granulation tissue (at 1 month and 3 months) in carotid arteries sprinkled with talcum powder and wrapped with perivascular PU film relative to a control group in which arteries are wrapped with perivascular PU film only.

DETAILED DESCRIPTION OF THE INVENTION

[0052] Definitions

[0053] Prior to setting forth the invention, it may be helpful to an understanding thereof to first set forth definitions of certain terms that is used hereinafter.

[0054] "Medical device", "implant", "medical device or implant", "implant/device", "the device", and the like are used synonymously to refer to any object that is designed to be placed partially or wholly within a patient's body for one or more therapeutic or prophylactic purposes such as for restoring physiological function, alleviating symptoms associated with disease, delivering therapeutic agents, and/or repairing or replacing or augmenting etc. damaged or diseased organs and tissues. While medical devices are normally composed of biologically compatible synthetic materials (e.g., medical-grade stainless steel, titanium and other metals; exogenous polymers, such as polyurethane, silicon, PLA, PLGA), other materials may also be used in the construction of the medical device or implant. Specific medical devices and implants that are particularly useful for the practice of this invention include devices and implants that are used to provide electrical stimulation to the central and peripheral nervous system (including the autonomic system), cardiac muscle tissue (including myocardial conduction pathways), smooth muscle tissue and skeletal muscle tissue.

[0055] "Electrical device" refers to a medical device having electrical components that can be placed in contact with tissue in an animal host and can provide electrical excitation to nervous or muscular tissue. Electrical devices can generate electrical impulses and may be used to treat many bodily dysfunctions and disorders by blocking, masking, or stimulating electrical signals within the body. Electrical medical devices of particular utility in the present invention include, but are not restricted to, devices used in the treatment of cardiac rhythm abnormalities, pain relief, epilepsy, Parkinson's Disease, movement disorders, obesity, depression, anxiety and hearing loss.

[0056] "Neurostimulator" or "Neurostimulation Device" refers to an electrical device for electrical excitation of the central, autonomic, or peripheral nervous system. The neurostimulator sends electrical impulses to an organ or tissue. The neurostimulator may include electrical leads as part of the electrical stimulation system. Neurostimulation may be used to block, mask, or stimulate electrical signals in the body to treat dysfunctions, including, without limitation, pain, seizures, anxiety disorders, depression, ulcers, deep vein thrombosis, muscular atrophy, obesity, joint stiffness, muscle spasms, osteoporosis, scoliosis, spinal disc degeneration, spinal cord injury, deafness, urinary dysfunction and gastroparesis. Neurostimulation may be delivered to many different parts of the nervous system, including, spinal cord, brain, vagus nerve, sacral nerve, gastric nerve, auditory nerves, as well as organs, bone, muscles and tissues. As

such, neurostimulators are developed to conform to the different anatomical structures and nervous system characteristics.

[0057] "Cardiac Stimulation Device" or "Cardiac Rhythm Management Device" or "Cardiac Pacemaker" or "Implantable Cardiac Defibrillator (ICD)" all refer to an electrical device for electrical excitation of cardiac muscle tissue (including the specialized cardiac muscle cells that make up the conductive pathways of the heart). The cardiac pacemaker sends electrical impulses to the muscle (myocardium) or conduction tissue of the heart. The pacemaker may include electrical leads as part of the electrical stimulation system. Cardiac pacemakers may be used to block, mask, or stimulate electrical signals in the heart to treat dysfunctions, including, without limitation, atrial rhythm abnormalities, conduction abnormalities and ventricular rhythm abnormalities.

[0058] "Electrical lead" refers to an electrical device that is used as a conductor to carry electrical signals from the generator to the tissues. Typically, electrical leads are composed of a connector assembly, a lead body (i.e., conductor) and an electrode. The electrical lead may be a wire or other material that transmits electrical impulses from a generator (e.g., pacemaker, defibrillator, or other neurostimulator). Electrical leads may be unipolar, in which they are adapted to provide effective therapy with only one electrode. Multipolar leads are also available, including bipolar, tripolar and quadripolar leads.

[0059] "Fibrosis" or "Scarring" refers to the formation of fibrous (scar) tissue (or in the case of injury in the CNS—the formation of glial tissue, or "gliosis", by astrocytes) in response to injury or medical intervention. Therapeutic agents which inhibit fibrosis or scarring can do so through one or more mechanisms including: inhibiting angiogenesis, inhibiting migration or proliferation of connective tissue cells (such as fibroblasts, smooth muscle cells, vascular smooth muscle cells), reducing ECM production, and/or inhibiting tissue remodeling. Therapeutic agents which inhibit gliosis can do so through one or more mechanisms including: inhibiting migration of glial cells, inhibition of hypertrophy of glial cells, and/or inhibiting proliferation of glial cells. In addition, numerous therapeutic agents described in this invention may have the additional benefit of also reducing tissue regeneration (the replacement of injured cells by cells of the same type) when appropriate.

[0060] "Inhibit fibrosis", "reduce fibrosis", "inhibit gliosis", "reduce gliosis" and the like are used synonymously to refer to the action of agents or compositions which result in a statistically significant decrease in the formation of fibrous or glial tissue that may be expected to occur in the absence of the agent or composition.

[0061] "Inhibitor" refers to an agent which prevents a biological process from occurring or slows the rate or degree of occurrence of a biological process. The process may be a general one such as scarring or refer to a specific biological action such as, for example, a molecular process resulting in release of a cytokine.

[0062] "Antagonist" refers to an agent which prevents a biological process from occurring or slows the rate or degree of occurrence of a biological process. While the process may be a general one, typically this refers to a drug mechanism where the drug competes with a molecule for an active molecular site or prevents a molecule from interacting with the molecular site. In these situations, the effect is that the molecular process is inhibited.

[0063] "Agonist" refers to an agent which stimulates a biological process or rate or degree of occurrence of a biological process. The process may be a general one such as scarring or refer to a specific biological action such as, for example, a molecular process resulting in release of a cytokine.

[0064] "Anti-microtubule agents" should be understood to include any protein, peptide, chemical, or other molecule which impairs the function of microtubules, for example, through the prevention or stabilization of polymerization. Compounds that stabilize polymerization of microtubules are referred to herein as "microtubule stabilizing agents." A wide variety of methods may be utilized to determine the anti-microtubule activity of a particular compound, including for example, assays described by Smith et al. (*Cancer Lett.* 79(2):213-219, 1994) and Mooberry et al., (*Cancer Lett.* 96(2):261-266, 1995).

[0065] "Host", "Person", "Subject", "Patient" and the like are used synonymously to refer to the living being (human or animal) into which a device of the present invention is implanted.

[0066] "Implanted" refers to having completely or partially placed a device within a host. A device is partially implanted when some of the device reaches, or extends to the outside of, a host.

[0067] "Release of an agent" refers to a statistically significant presence of the agent, or a subcomponent thereof, which has disassociated from the implant/device and/or remains active on the surface of (or within) the device/implant.

[0068] "Biodegradable" refers to materials for which the degradation process is at least partially mediated by, and/or performed in, a biological system. "Degradation" refers to a chain scission process by which a polymer chain is cleaved into oligomers and monomers. Chain scission may occur through various mechanisms, including, for example, by chemical reaction (e.g., hydrolysis) or by a thermal or photolytic process. Polymer degradation may be characterized, for example, using gel permeation chromatography (GPC), which monitors the polymer molecular mass changes during erosion and drug release. Biodegradable also refers to materials may be degraded by an erosion process mediated by, and/or performed in, a biological system. "Erosion" refers to a process in which material is lost from the bulk. In the case of a polymeric system, the material may be a monomer, an oligomer, a part of a polymer backbone, or a part of the polymer bulk. Erosion includes (i) surface erosion, in which erosion affects only the surface and not the inner parts of a matrix; and (ii) bulk erosion, in which the entire system is rapidly hydrated and polymer chains are cleaved throughout the matrix. Depending on the type of polymer, erosion generally occurs by one of three basic mechanisms (see, e.g., Heller, J., *CRC Critical Review in Therapeutic Drug Carrier Systems* (1984), 1(1), 39-90); Siepmann, J. et al., *Adv. Drug Del. Rev.* (2001), 48, 229-247): (1) water-soluble polymers that have been insolubilized by covalent cross-links and that solubilize as the

cross-links or the backbone undergo a hydrolytic cleavage; (2) polymers that are initially water insoluble are solubilized by hydrolysis, ionization, or pronation of a pendant group; and (3) hydrophobic polymers are converted to small water-soluble molecules by backbone cleavage. Techniques for characterizing erosion include thermal analysis (e.g., DSC), X-ray diffraction, scanning electron microscopy (SEM), electron paramagnetic resonance spectroscopy (EPR), NMR imaging, and recording mass loss during an erosion experiment. For microspheres, photon correlation spectroscopy (PCS) and other particles size measurement techniques may be applied to monitor the size evolution of erodible devices versus time.

[0069] As used herein, "analogue" refers to a chemical compound that is structurally similar to a parent compound, but differs slightly in composition (e.g., one atom or functional group is different, added, or removed). The analogue may or may not have different chemical or physical properties than the original compound and may or may not have improved biological and/or chemical activity. For example, the analogue may be more hydrophilic or it may have altered reactivity as compared to the parent compound. The analogue may mimic the chemical and/or biologically activity of the parent compound (i.e., it may have similar or identical activity), or, in some cases, may have increased or decreased activity. The analogue may be a naturally or non-naturally occurring (e.g., recombinant) variant of the original compound. An example of an analogue is a mutein (i.e., a protein analogue in which at least one amino acid is deleted, added, or substituted with another amino acid). Other types of analogues include isomers (enantiomers, diasteromers, and the like) and other types of chiral variants of a compound, as well as structural isomers. The analogue may be a branched or cyclic variant of a linear compound. For example, a linear compound may have an analogue that is branched or otherwise substituted to impart certain desirable properties (e.g., improve hydrophilicity or bioavailability).

[0070] As used herein, "derivative" refers to a chemically or biologically modified version of a chemical compound that is structurally similar to a parent compound and (actually or theoretically) derivable from that parent compound. A "derivative" differs from an "analogue" in that a parent compound may be the starting material to generate a "derivative," whereas the parent compound may not necessarily be used as the starting material to generate an "analogue." A derivative may or may not have different chemical or physical properties of the parent compound. For example, the derivative may be more hydrophilic or it may have altered reactivity as compared to the parent compound. Derivatization (i.e., modification) may involve substitution of one or more moieties within the molecule (e.g., a change in functional group). For example, a hydrogen may be substituted with a halogen, such as fluorine or chlorine, or a hydroxyl group (—OH) may be replaced with a carboxylic acid moiety (—COOH). The term "derivative" also includes conjugates, and prodrugs of a parent compound (i.e., chemically modified derivatives which can be converted into the original compound under physiological conditions). For example, the prodrug may be an inactive form of an active agent. Under physiological conditions, the prodrug may be converted into the active form of the compound. Prodrugs may be formed, for example, by replacing one or two hydrogen atoms on nitrogen atoms by an acyl group (acyl prodrugs) or a carbamate group (carbamate prodrugs). More detailed information relating to prodrugs is found, for example, in Fleisher et al., *Advanced Drug Delivery Reviews* 19 (1996) 115; *Design of Prodrugs*, H. Bundgaard (ed.), Elsevier, 1985; or H. Bundgaard, *Drugs of the Future* 16 (1991) 443. The term "derivative" is also used to describe all solvates, for example hydrates or adducts (e.g., adducts with alcohols), active metabolites, and salts of the parent compound. The type of salt that may be prepared depends on the nature of the moieties within the compound. For example, acidic groups, for example carboxylic acid groups, can form, for example, alkali metal salts or alkaline earth metal salts (e.g., sodium salts, potassium salts, magnesium salts and calcium salts, and also salts with physiologically tolerable quaternary ammonium ions and acid addition salts with ammonia and physiologically tolerable organic amines such as, for example, triethylamine, ethanolamine or tris-(2-hydroxyethyl)amine). Basic groups can form acid addition salts, for example with inorganic acids such as hydrochloric acid, sulfuric acid or phosphoric acid, or with organic carboxylic acids and sulfonic acids such as acetic acid, citric acid, benzoic acid, maleic acid, fumaric acid, tartaric acid, methanesulfonic acid or p-toluenesulfonic acid. Compounds which simultaneously contain a basic group and an acidic group, for example a carboxyl group in addition to basic nitrogen atoms, can be present as zwitterions. Salts can be obtained by customary methods known to those skilled in the art, for example by combining a compound with an inorganic or organic acid or base in a solvent or diluent, or from other salts by cation exchange or anion exchange.

[0071] Any concentration ranges, percentage range, or ratio range recited herein are to be understood to include concentrations, percentages or ratios of any integer within that range and fractions thereof, such as one tenth and one hundredth of an integer, unless otherwise indicated. Also, any number range recited herein relating to any physical feature, such as polymer subunits, size or thickness, are to be understood to include any integer within the recited range, unless otherwise indicated. It should be understood that the terms "a" and "an" as used above and elsewhere herein refer to "one or more" of the enumerated components. For example, "a" polymer refers to one polymer or a mixture comprising two or more polymers. As used herein, the term "about" means±15%.

[0072] As discussed above, the present invention provides compositions, methods and devices relating to medical devices and implants, which greatly increase their ability to inhibit the formation of reactive scar (or glial) tissue on, or around, the surface of the device or implant. Described in more detail below are methods for constructing medical devices or implants, compositions and methods for generating medical devices and implants which inhibit fibrosis, and methods for utilizing such medical devices and implants.

[0073] A. Clinical Applications of Electrical Medical Devices and Implants Which Contain a Fibrosis-inhibiting Agent

[0074] Medical devices having electrical components, such as electrical pacing or stimulating devices, can be implanted in the body to provide electrical conduction to the central and peripheral nervous system (including the autonomic system), cardiac muscle tissue (including myocardial conduction pathways), smooth muscle tissue and skeletal

muscle tissue. These electrical impulses are used to treat many bodily dysfunctions and disorders by blocking, masking, stimulating, or replacing electrical signals within the body. Examples include pacemaker leads used to maintain the normal rhythmic beating of the heart; defibrillator leads used to "re-start" the heart when it stops beating; peripheral nerve stimulating devices to treat chronic pain; deep brain electrical stimulation to treat conditions such as tremor, Parkinson's disease, movement disorders, epilepsy, depression and psychiatric disorders; and vagal nerve stimulation to treat epilepsy, depression, anxiety, obesity, migraine and Alzheimer's Disease.

[0075] The clinical function of an electrical device such as a cardiac pacemaker lead, neurostimulation lead, or other electrical lead depends upon the device being able to effectively maintain intimate anatomical contact with the target tissue (typically electrically excitable cells such as muscle or nerve) such that electrical conduction from the device to the tissue can occur. Unfortunately, in many instances when these devices are implanted in the body, they are subject to a "foreign body" response from the surrounding host tissues. The body recognizes the implanted device as foreign, which triggers an inflammatory response followed by encapsulation of the implant with fibrous connective tissue (or glial tissue—called "gliosis"—when it occurs within the central nervous system). Scarring (i.e., fibrosis or gliosis) can also result from trauma to the anatomical structures and tissue surrounding the implant during the implantation of the device. Lastly, fibrous encapsulation of the device can occur even after a successful implantation if the device is manipulated (some patients continuously "fiddle" with a subcutaneous implant) or irritated by the daily activities of the patient. When scarring occurs around the implanted device, the electrical characteristics of the electrode-tissue interface degrade, and the device may fail to function properly. For example, it may require additional electrical current from the lead to overcome the extra resistance imposed by the intervening scar (or glial) tissue. This can shorten the battery life of an implant (making more frequent removal and re-implantation necessary), prevent electrical conduction altogether (rendering the implant clinically ineffective) and/or cause damage to the target tissue. Additionally, the surrounding tissue may be inadvertently damaged from the inflammatory foreign body response, which can result in loss of function or tissue necrosis.

[0076] The present invention addresses these problems. Exemplary electrical devices are described next.

[0077] 1) Neurostimulation Devices

[0078] In one aspect, the electrical device may be a neurostimulation device where a pulse generator delivers an electrical impulse to a nervous tissue (e.g., CNS, peripheral nerves, autonomic nerves) in order to regulate its activity. There are numerous neurostimulator devices where the occurrence of a fibrotic reaction may adversely affect the functioning of the device or the biological problem for which the device was implanted or used. Typically, fibrotic encapsulation of the electrical lead (or the growth of fibrous tissue between the lead and the target nerve tissue) slows, impairs, or interrupts electrical transmission of the impulse from the device to the tissue. This can cause the device to function suboptimally or not at all, or can cause excessive drain on battery life because increased energy is required to overcome the electrical resistance imposed by the intervening scar (or glial) tissue.

[0079] Neurostimulation devices are used as alternative or adjunctive therapy for chronic, neurodegenerative diseases, which are typically treated with drug therapy, invasive therapy, or behavioral/lifestyle changes. Neurostimulation may be used to block, mask, or stimulate electrical signals in the body to treat dysfunctions, including, without limitation, pain, seizures, anxiety disorders, depression, ulcers, deep vein thrombosis, muscular atrophy, obesity, joint stiffness, muscle spasms, osteoporosis, scoliosis, spinal disc degeneration, spinal cord injury, deafness, urinary dysfunction and gastroparesis. Neurostimulation may be delivered to many different parts of the nervous system, including, spinal cord, brain, vagus nerve, sacral nerve, gastric nerve, auditory nerves, as well as organs, bone, muscles and tissues. As such, neurostimulators are developed to conform to the different anatomical structures and nervous system characteristics. Representative examples of neurologic and neurosurgical implants and devices that can be coated with, or otherwise constructed to contain and/or release the therapeutic agents provided herein, include, e.g., nerve stimulator devices to provide pain relief, devices for continuous subarachnoid infusions, implantable electrodes, stimulation electrodes, implantable pulse generators, electrical leads, stimulation catheter leads, neurostimulation systems, electrical stimulators, cochlear implants, auditory stimulators and microstimulators.

[0080] Neurostimulation devices may also be classified based on their source of power, which includes: battery powered, radio-frequency (RF) powered, or a combination of both types. For battery powered neurostimulators, an implanted, non-rechargeable battery is used for power. The battery and leads are all surgically implanted and thus the neurostimulation device is completely internal. The settings of the totally implanted neurostimulator are controlled by the patient through an external magnet. The lifetime of the implant is generally limited by the duration of battery life and ranges from two to four years depending upon usage and power requirements. For RF-powered neurostimulation devices, the radio-frequency is transmitted from an externally worn source to an implanted passive receiver. Since the power source is readily rechargeable or replaceable, the radio-frequency system enables greater power resources and thus, multiple leads may be used in these systems. Specific examples include a neurostimulator that has a battery power source contained within to supply power over an eight hour period in which power may be replenished by an external radio frequency coupled device (See e.g., U.S. Pat. No. 5,807,397) or a microstimulator which is controlled by an external transmitter using data signals and powered by radio frequency (See e.g., U.S. Pat. No. 6,061,596).

[0081] Examples of commercially available neurostimulation products include a radio-frequency powered neurostimulator comprised of the 3272 MATTRIX Receiver, 3210 MATTRIX Transmitter and 3487A PISCES-QUAD Quadripolar Leads made by Medtronic, Inc. (Minneapolis, Minn.). Medtronic also sells a battery-powered ITREL 3 Neurostimulator and SYNERGY Neurostimulator, the INTERSIM Therapy for sacral nerve stimulation for urinary control, and leads such as the 3998 SPECIFY Lead and 3587A RESUME II Lead.

[0082] Another example of a neurostimulation device is a gastric pacemaker, in which multiple electrodes are positioned along the GI tract to deliver a phased electrical stimulation to pace peristaltic movement of the material through the GI tract. See, e.g., U.S. Pat. No. 5,690,691. A representative example of a gastric stimulation device is the ENTERRA Gastric Electrical Stimulation (GES) from Medtronic, Inc. (Minneapolis, Minn.).

[0083] The neurostimulation device, particularly the lead(s), must be positioned in a very precise manner to ensure that stimulation is delivered to the correct anatomical location in the nervous system. All, or parts, of a neurostimulation device can migrate following surgery, or excessive scar (or glial) tissue growth can occur around the implant, which can lead to a reduction in the performance of these devices (as described previously). Neurostimulator devices that release a therapeutic agent for reducing scarring (or gliosis) at the electrode-tissue interface can be used to increase the efficacy and/or the duration of activity (particularly for fully-implanted, battery-powered devices) of the implant. Accordingly, the present invention provides neurostimulator leads that are coated with an anti-scarring agent or a composition that includes an anti-scarring (or anti-gliosis) agent.

[0084] For greater clarity, several specific neurostimulation devices and treatments will be described in greater detail including:

[0085] a) Neurostimulation for the Treatment of Chronic Pain

[0086] Chronic pain is one of the most important clinical problems in all of medicine. For example, it is estimated that over 5 million people in the United States are disabled by back pain. The economic cost of chronic back pain is enormous, resulting in over 100 million lost work days annually at an estimated cost of $50-100 billion. It has been reported that approximately 40 million Americans are afflicted with recurrent headaches and that the cost of medications for this condition exceeds $4 billion a year. A further 8 million people in the U.S. report that they experience chronic neck or facial pain and spend an estimated $2 billion a year for treatment. The cost of managing pain for oncology patients is thought to approach $12 billion. Chronic pain disables more people than cancer or heart disease and costs the American public more than both cancer and heart disease combined. In addition to the physical consequences, chronic pain has numerous other costs including loss of employment, marital discord, depression and prescription drug addiction. It goes without saying, therefore, that reducing the morbidity and costs associated with persistent pain remains a significant challenge for the healthcare system.

[0087] Intractable severe pain resulting from injury, illness, scoliosis, spinal disc degeneration, spinal cord injury, malignancy, arachnoiditis, chronic disease, pain syndromes (e.g., failed back syndrome, complex regional pain syndrome) and other causes is a debilitating and common medical problem. In many patients, the continued use of analgesics, particularly drugs like narcotics, are not a viable solution due to tolerance, loss of effectiveness, and addiction potential. In an effort to combat this, neurostimulation devices have been developed to treat severe intractable pain that is resistant to other traditional treatment modalities such as drug therapy, invasive therapy (surgery), or behavioral/lifestyle changes.

[0088] In principle, neurostimulation works by delivering low voltage electrical stimulation to the spinal cord or a particular peripheral nerve in order to block the sensation of pain. The Gate Control Theory of Pain (Ronald Meizack and Patrick Wall) hypothesizes that there is a "gate" in the dorsal horn of the spinal cord that controls the flow of pain signals from the peripheral receptors to the brain. It is speculated that the body can inhibit the pain signals ("close the gate") by activating other (non-pain) fibers in the region of the dorsal horn. Neurostimulation devices are implanted in the epidural space of the spinal cord to stimulate non-noxious nerve fibers in the dorsal horn and mask the sensation of pain. As a result the patient typically experiences a tingling sensation (known as paresthesia) instead of pain. With neurostimulation, the majority of patients will report improved pain relief (50% reduction), increased activity levels and a reduction in the use of narcotics.

[0089] Pain management neurostimulation systems consist of a power source that generates the electrical stimulation, leads (typically 1 or 2) that deliver electrical stimulation to the spinal cord or targeted peripheral nerve, and an electrical connection that connects the power source to the leads. Neurostimulation systems can be battery powered, radio-frequency powered, or a combination of both. In general, there are two types of neurostimulation devices: those that are surgically implanted and are completely internal (i.e., the battery and leads are implanted), and those with internal (leads and radio-frequency receiver) and external (power source and antenna) components. For internal, battery-powered neurostimulators, an implanted, non-rechargeable battery and the leads are all surgically implanted. The settings of the totally implanted neurostimulator may be controlled by the host by using an external magnet and the implant has a lifespan of two to four years. For radio-frequency powered neurostimulators, the radio-frequency is transmitted from an externally worn source to an implanted passive receiver. The radio-frequency system enables greater power resources and thus, multiple leads may be used.

[0090] There are numerous neurostimulation devices that can be used for spinal cord stimulation in the management of pain control, postural positioning and other disorders. Examples of specific neurostimulation devices include those composed of a sensor that detects the position of the spine and a stimulator that automatically emits a series of pulses which decrease in amplitude when back is in a supine position. See e.g., U.S. Pat. Nos. 5,031,618 and 5,342,409. The neurostimulator may be composed of electrodes and a control circuit which generates pulses and rest periods based on intervals corresponding to the body's activity and regeneration period as a treatment for pain. See e.g., U.S. Pat. No. 5,354,320. The neurostimulator, which may be implanted within the epidural space parallel to the axis of the spinal cord, may transmit data to a receiver which generates a spinal cord stimulation pulse that may be delivered via a coupled, multi-electrode. See e.g., U.S. Pat. No. 6,609,031. The neurostimulator may be a stimulation catheter lead with a sheath and at least three electrodes that provide stimulation to neural tissue. See e.g., U.S. Pat. No. 6,510,347. The neurostimulator may be a self-centering epidual spinal cord

lead with a pivoting region to stabilize the lead which inflates when injected with a hardening agent. See e.g., U.S. Pat. No. 6,308,103. Other neurostimulators used to induce electrical activity in the spinal cord are described in, e.g., U.S. Pat. Nos. 6,546,293; 6,236,892; 4,044,774 and 3,724,467.

[0091] Commercially available neurostimulation devices for the management of chronic pain include the SYNERGY, INTREL, X-TREL and MATTRIX neurostimulation systems from Medtronic, Inc. The percutaneous leads in this system can be quadripolar (4 electrodes), such as the PISCES-QUAD, PISCES-QUAD PLUS and the PISCES-QUAD Compact, or octapolar (8 electrodes) such as the OCTAD lead. The surgical leads themselves are quadripolar, such as the SPECIFY Lead, the RESUME II Lead, the RESUME TL Lead and the ON-POINT PNS Lead, to create multiple stimulation combinations and a broad area of paresthesia. These neurostimulation systems and associated leads may be described, for example, in U.S. Pat. Nos. 6,671,544; 6,654,642; 6,360,750; 6,353,762; 6,058,331; 5,342,409; 5,031,618 and 4,044,774. Neurostimulating leads such as these may benefit from release of a therapeutic agent able to reducing scarring at the electrode-tissue interface to increase the efficiency of impulse transmission and increase the duration that the leads function clinically. In one aspect, the device includes spinal cord stimulating devices and/or leads that are coated with an anti-scarring (or anti-gliosis) agent or a composition that includes an anti-scarring (or anti-gliosis) agent. As an alternative to this, or in addition to this, a composition that includes an anti-scarring agent can be infiltrated into the epidural space where the lead will be implanted. Other commercially available systems that may useful for the practice of this invention as described above include the rechargeable PRECISION Spinal Cord Stimulation System (Advanced Bionics Corporation, Sylmar, Calif.; which is a Boston Scientific Company) which can drive up to 16 electrodes (see e.g., U.S. Pat. Nos. 6,735,474; 6,735,475; 6,659,968; 6,622,048; 6,516,227 and 6,052,624). The GENESIS XP Spinal Cord Stimulator available from Advanced Neuromodulation Systems, Inc. (Plano, Tex.; see e.g., U.S. Pat. Nos. 6,748,276; 6,609,031 and 5,938,690) as well as the Vagus Nerve Stimulation (VNS) Therapy System available from Cyberonics, Inc. (Houston, Tex.; see e.g., U.S. Pat. Nos. 6,721,603 and 5,330,515) may also benefit from the application of anti-fibrosis (or anti-gliosis) agents as described in this invention.

[0092] Regardless of the specific design features, for neurostimulation to be effective in pain relief, the leads must be accurately positioned adjacent to the portion of the spinal cord or the targeted peripheral nerve that is to be electrically stimulated. Neurostimulators can migrate following surgery or excessive tissue growth or extracellular matrix deposition can occur around neurostimulators, which can lead to a reduction in the functioning of these devices. Neurostimulator devices that release therapeutic agent for reducing scarring at the electrode-tissue interface can be used to increase the duration that these devices clinically function. In one aspect, the device includes neurostimulator devices and/or leads that are coated with an anti-scarring (or anti-gliosis) agent or a composition that includes an anti-scarring (or anti-gliosis) agent. As an alternative to this, or in addition to this, a composition that includes an anti-scarring (anti-gliosis) agent can be infiltrated into the tissue surrounding the implanted portion (particularly the leads) of the pain management neurostimulation device.

[0093] b) Neurostimulation for the Treatment of Parkinson's Disease

[0094] Neurostimulation devices implanted into the brain are used to control the symptoms associated with Parkinson's disease or essential tremor. Typically, these are dual chambered stimulator devices (similar to cardiac pacemakers) that deliver bilateral stimulation to parts of the brain that control motor function. Electrical stimulation is used to relieve muscular symptoms due to Parkinson's disease itself (tremor, rigidity, bradykinesia, akinesia) or symptoms that arise as a result of side effects of the medications used to treat the disease (dyskinesias). Two stimulating electrodes are implanted in the brain (usually bilaterally in the subthalamic nucleus or the globus pallidus interna) for the treatment of levodopa-responsive Parkinson's and one is implanted (in the ventral intermediate nucleus of the thalamus) for the treatment of tremor. The electrodes are implanted in the brain by a functional stereotactic neurosurgeon using a stereotactic head frame and MRI or CT guidance. The electrodes are connected via extensions (which run under the skin of the scalp and neck) to a neurostimulatory (pulse generating) device implanted under the skin near the clavicle. A neurologist can then optimize symptom control by adjusting stimulation parameters using a noninvasive control device that communicates with the neurostimulator via telemetry. The patient is also able to turn the system on and off using a magnet and control the device (within limits set by the neurologist) settings using a controller device. This form of deep brain stimulation has also been investigated for the treatment pain, epilepsy, psychiatric conditions (obsessive-compulsive disorder) and dystonia.

[0095] Several devices have been described for such applications including, for example, a neurostimulator and an implantable electrode that has a flexible, non-conducting covering material, which is used for tissue monitoring and stimulation of the cortical tissue of the brain as well as other tissue. See e.g., U.S. Pat. No. 6,024,702. The neurostimulator (pulse generator) may be an intracranially implanted electrical control module and a plurality of electrodes which stimulate the brain tissue with an electrical signal at a defined frequency. See e.g., U.S. Pat. No. 6,591,138. The neurostimulator may be a system composed of at least two electrodes adapted to the cranium and a control module adapted to be implanted beneath the scalp for transmitting output electrical signals and also external equipment for providing two-way communication. See e.g., U.S. Pat. No. 6,016,449. The neurostimulator may be an implantable assembly composed of a sensor and two electrodes, which are used to modify the electrical activity in the brain. See e.g., U.S. Pat. No. 6,466,822.

[0096] A commercial example of a device used to treat Parkinson's disease and essential tremor includes the ACTIVA System by Medtronic, Inc. (see, for example, U.S. Pat. Nos. 6,671,544 and 6,654,642). This system consists of the KINETRA Dual Chamber neurostimulator, the SOLETRA neurostimulator or the INTREL neurostimulator, connected to an extension (an insulated wire), that is further connected to a DBS lead. The DBS lead consists of four thin, insulated, coiled wires bundled with polyurethane. Each of

the four wires ends in a 1.5 mm long electrode. Although all or parts of the DBS lead may be suitable for coating with a fibrosis/gliosis-inhibiting composition, a preferred embodiment involves delivering the therapeutic agent from the surface of the four electrodes. As an alternative to this, or in addition to this, a composition that includes an anti-gliosis agent can be infiltrated into the brain tissue surrounding the leads.

[0097] c) Vagal Nerve Stimulation for the Treatment of Epilepsy

[0098] Neurostimulation devices are also used for vagal nerve stimulation in the management of pharmacoresistant epilepsy (i.e., epilepsy that is uncontrolled despite appropriate medical treatment with ant-epileptic drugs). Approximately 30% of epileptic patients continue to have seizures despite of multiple attempts at controlling the disease with drug therapy or are unable to tolerate the side effects of their medications. It is estimated that approximately 2.5 million patients in the United States suffer from treatment-resistant epilepsy and may benefit from vagal nerve stimulation therapy. As such, inadequate seizure control remains a significant medical problem with many patients suffering from diminished self esteem, poor academic achievement and a restricted lifestyle as a result of their illness.

[0099] The vagus nerve (also called the 10^{th} cranial nerve) contains primarily afferent sensory fibres that carry information from the neck, thorax and abdomen to the nucleus tractus soltarius of the brainstem and on to multiple noradrenergic and serotonergic neuromodulatory systems in the brain and spinal cord. Vagal nerve stimulation (VNS) has been shown to induce progressive EEG changes, alter bilateral cerebral blood flow, and change blood flow to the thalamus. Although the exact mechanism of seizure control is not known, VNS has been demonstrated clinically to terminate seizures after seizure onset, reduce the severity and frequency of seizures, prevent seizures when used prophylactically over time, improve quality of life, and reduce the dosage, number and side effects of anti-epileptic medications (resulting in improved alertness, mood, memory).

[0100] In VNS, a bipolar electrical lead is surgically implanted such that it transmits electrical stimulation from the pulse generator to the left vagus nerve in the neck. The pulse generator is an implanted, lithium carbon monofluoride battery-powered device that delivers a precise pattern of stimulation to the vagus nerve. The pulse generator can be programmed (using a programming wand) by the neurologist to suit an individual patient's symptoms, while the patient can turn the device on and off through the use of an external magnet. Chronic electrical stimulation which can be used as a direct treatment for epilepsy is described in, for example, U.S. Pat. No. 6,016,449, whereby, an implantable neurostimulator is coupled to relatively permanent deep brain electrodes. The implantable neurostimulator may be composed of an implantable electrical lead having a furcated, or split, distal portion with two or more separate end segments, each of which bears at least one sensing or stimulation electrode, which may be used to treat epilepsy and other neurological disorders. See e.g., U.S. Pat. No. 6,597,953.

[0101] A commercial example of a VNS system is the product produced by Cyberonics, Inc. that includes the Model 300 and Model 302 leads, the Model 101 and Model 102R pulse generators, the Model 201 programming wand and Model 250 programming software, and the Model 220 magnets. These products manufactured by Cyberonics, Inc. may be described, for example, in U.S. Pat. Nos. 5,540,730 and 5,299,569.

[0102] Regardless of the specific design features, for vagal nerve stimulation to be effective in epilepsy, the leads must be accurately positioned adjacent to the left vagus nerve. If excessive scar tissue growth or extracellular matrix deposition occurs around the VNS leads, this can reduce the efficacy of the device. VNS devices that release a therapeutic agent able to reducing scarring at the electrode-tissue interface can increase the efficiency of impulse transmission and increase the duration that these devices function clinically. In one aspect, the device includes VNS devices and/or leads that are coated with an anti-scarring agent or a composition that includes an anti-scarring agent. As an alternative to this, or in addition to this, a composition that includes an anti-scarring agent can be infiltrated into the tissue surrounding the vagus nerve where the lead will be implanted.

[0103] d) Vagal Nerve Stimulation for the Treatment of Other Disorders

[0104] It was discovered during the use of VNS for the treatment of epilepsy that some patients experienced an improvement in their mood during therapy. As such, VNS is currently being examined for use in the management of treatment-resistant mood disorders such as depression and anxiety. Depression remains an enormous clinical problem in the Western World with over 1% (25 million people in the United States) suffering from depression that is inadequately treated by pharmacotherapy. Vagal nerve stimulation has been examined in the management of conditions such as anxiety (panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder), obesity, migraine, sleep disorders, dementia, Alzheimer's disease and other chronic or degenerative neurological disorders. VNS has also been examined for use in the treatment of medically significant obesity.

[0105] The implantable neurostimulator for the treatment of neurological disorders may be composed of an implantable electrical lead having a furcated, or split, distal portion with two or more separate end segments, each of which bears at least one sensing or stimulation electrode. See e.g., U.S. Pat. No. 6,597,953. The implantable neurostimulator may be an apparatus for treating Alzheimer's disease and dementia, particularly for neuro modulating or stimulating left vagus nerve, composed of an implantable lead-receiver, external stimulator, and primary coil. See e.g., U.S. Pat. No. 6,615,085.

[0106] Cyberonics, Inc. manufactures the commercially available VNS system, including the Model 300 and Model 302 leads, the Model 101 and Model 102R pulse generators, the Model 201 programming wand and Model 250 programming software, and the Model 220 magnets. These products as well as others that are being developed by Cyberonics, Inc. may be used to treat neurological disorders, including depression (see e.g., U.S. Pat. No. 5,299,569), dementia (see e.g., U.S. Pat. No. 5,269,303), migraines (see e.g., U.S. Pat. No. 5,215,086), sleep disorders (see e.g., U.S. Pat. No. 5,335,657) and obesity (see e.g., U.S. Pat. Nos. 6,587,719; 6,609,025; 5,263,480 and 5,188,104).

[0107] It is important to note that the fundamentals of treatment are identical to those described above for epilepsy. The devices employed and the principles of therapy are also similar. As was described above for the treatment of epilepsy, if excessive scar tissue growth or extracellular matrix deposition occurs around the VNS leads, this can reduce the efficacy of the device. VNS devices that release a therapeutic agent able to reducing scarring at the electrode-tissue interface can increase the efficiency of impulse transmission and increase the duration that these devices function clinically for the treatment of depression, anxiety, obesity, sleep disorders and dementia. In one aspect, the device includes VNS devices and/or leads that are coated with an anti-scarring agent or a composition that includes an anti-scarring agent. As an alternative to this, or in addition to this, a composition that includes an anti-scarring agent can be infiltrated into the tissue surrounding the vagus nerve where the lead will be implanted.

[0108] e) Sacral Nerve Stimulation for Bladder Control Problems

[0109] Sacral nerve stimulation is used in the management of patients with urinary control problems such as urge incontinence, nonobstructive urinary retention, or urgency-frequency. Millions of people suffer from bladder control problems and a significant percentage (estimated to be in excess of 60%) is not adequately treated by other available therapies such as medications, absorbent pads, external collection devices, bladder augmentation or surgical correction. This can be a debilitating medical problem that can cause severe social anxiety and cause people to become isolated and depressed.

[0110] Mild electrical stimulation of the sacral nerve is used to influence the functioning of the bladder, urinary sphincter, and the pelvic floor muscles (all structures which receive nerve supply from the sacral nerve). An electrical lead is surgically implanted adjacent to the sacral nerve and a neurostimulator is implanted subcutaneously in the upper buttock or abdomen; the two are connected by an extension. The use of tined leads allows sutureless anchoring of the leads and minimally-invasive placement of the leads under local anesthesia. A handheld programmer is available for adjustment of the device by the attending physician and a patient-controlled programmer is available to adjust the settings and to turn the device on and off. The pulses are adjusted to provide bladder control and relieve the patient's symptoms.

[0111] Several neurostimulation systems have been described for sacral nerve stimulation in which electrical stimulation is targeted towards the bladder, pelvic floor muscles, bowel and/or sexual organs. For example, the neurostimulator may be an electrical stimulation system composed of an electrical stimulator and leads having insulator sheaths, which may be anchored in the sacrum using minimally-invasive surgery. See e.g., U.S. Pat. No. 5,957,965. In another aspect, the neurostimulator may be used to condition pelvic, sphincter or bladder muscle tissue. For example, the neurostimulator may be intramuscular electrical stimulator composed of a pulse generator and an elongated medical lead that is used for electrically stimulating or sensing electrical signals originating from muscle tissue. See e.g., U.S. Pat. No. 6,434,431. Another neurostimulation system consists of a leadless, tubular-shaped microstimulator that is implanted at pelvic floor muscles or associated nerve tissue that need to be stimulated to treat urinary incontinence. See e.g., U.S. Pat. No. 6,061,596.

[0112] A commercially available example of a neurostimulation system to treat bladder conditions is the INTERSTIM Sacral Nerve Stimulation System made by Medtronic, Inc. See e.g., U.S. Pat. Nos. 6,104,960; 6,055,456 and 5,957,965.

[0113] Regardless of the specific design features, for bladder control therapy to be effective, the leads must be accurately positioned adjacent to the sacral nerve, bladder, sphincter or pelvic muscle (depending upon the particular system employed). If excessive scar tissue growth or extracellular matrix deposition occurs around the leads, efficacy can be compromised. Sacral nerve stimulating devices (such as INTERSTIM) that release a therapeutic agent able to reducing scarring at the electrode-tissue interface can increase the efficiency of impulse transmission and increase the duration that these devices function clinically. In one aspect, the device includes sacral nerve stimulating devices and/or leads that are coated with an anti-scarring agent or a composition that includes an anti-scarring agent. As an alternative to this, or in addition to this, a composition that includes an anti-scarring agent can be infiltrated into the tissue surrounding the sacral nerve where the lead will be implanted.

[0114] For devices designed to stimulate the bladder or pelvic muscle tissue directly, slightly different embodiments may be required. In this aspect, the device includes bladder or pelvic muscle stimulating devices, leads, and/or sensors that are coated with an anti-scarring agent or a composition that includes an anti-scarring agent. As an alternative to this, or in addition to this, a composition that includes an anti-scarring agent can be directly infiltrated into the muscle tissue itself (preferably adjacent to the lead and/or sensor that is delivering an impulse or monitoring the activity of the muscle).

[0115] f) Gastric Nerve Stimulation for the Treatment of GI Disorders

[0116] Neurostimulator of the gastric nerve (which supplies the stomach and other portions of the upper GI tract) is used to influence gastric emptying and satiety sensation in the management of clinically significant obesity or problems associated with impaired GI motility. Morbid obesity has reached epidemic proportions and is thought to affect over 25 million Americans and lead to significant health problems such as diabetes, heart attack, stroke and death. Mild electrical stimulation of the gastric nerve is used to influence the functioning of the upper GI tract and stomach (all structures which receive nerve supply from the gastric nerve). An electrical lead is surgically implanted adjacent to the gastric nerve and a neurostimulator is implanted subcutaneously; the two are connected by an extension. A handheld programmer is available for adjustment of the device by the attending physician and a patient-controlled programmer is available to adjust the settings and to turn the device on and off. The pulses are adjusted to provide a sensation of satiety and relieve the sensation of hunger experienced by the patient. This can reduce the amount of food (and hence caloric) intake and allow the patient to lose weight successfully. Related devices include neurostimulation devices used to stimulate gastric emptying in patients with impaired

gastric motility, a neurostimulator to promote bowel evacuation in patients with constipation (stimulation is delivered to the colon), and devices targeted at the bowel for patients with other GI motility disorders.

[0117] Several such devices have been described including, for example, a sensor that senses electrical activity in the gastrointestinal tract which is coupled to a pulse generator that emits and inhibits asynchronous stimulation pulse trains based on the natural gastrointestinal electrical activity. See e.g., U.S. Pat. No. 5,995,872. Other neurostimulation devices deliver impulses to the colon and rectum to manage constipation and are composed of electrical leads, electrodes and an implanted stimulation generator. See e.g., U.S. Pat. No. 6,026,326. The neurostimulator may be a pulse generator and electrodes that electrically stimulate the neuromuscular tissue of the viscera to treat obesity. See e.g., U.S. Pat. No. 6,606,523. The neurostimulator may be a hermetically sealed implantable pulse generator that is electrically coupled to the gastrointestinal tract and emits two rates of electrical stimulation to treat gastroparesis for patients with impaired gastric emptying. See e.g., U.S. Pat. No. 6,091,992. The neurostimulator may be composed of an electrical signal controller, connector wire and attachment lead which generates continuous low voltage electrical stimulation to the fundus of the stomach to control appetite. See e.g., U.S. Pat. No. 6,564,101. Other neurostimulators that are used to electrically stimulate the gastrointestinal tract are described in, e.g., U.S. Pat. Nos. 6,453,199; 6,449,511 and 6,243,607.

[0118] Another example of a gastric nerve stimulation device for use with the present invention is the TRANSCEND Implantable Gastric Stimulator (IGS), which is currently being developed by Transneuronix, Inc. (Mt. Arlington, N.J.). The IGS is a programmable, bipolar pulse generator that delivers small bursts of electrical pulses through the lead to the stomach wall to treat obesity. See, e.g., U.S. Pat. Nos. 6,684,104 and 6,165,084.

[0119] Regardless of the specific design features, for gastric nerve stimulation to be effective in satiety control (or gastroparesis), the leads must be accurately positioned adjacent to the gastric nerve. If excessive scar tissue growth or extracellular matrix deposition occurs around the leads, efficacy can be compromised. Gastric nerve stimulating devices (and other implanted devices designed to influence GI motility) that release a therapeutic agent able to reduce scarring at the electrode-tissue interface can increase the efficiency of impulse transmission and increase the duration that these devices function clinically. In one aspect, the device includes gastric nerve stimulating devices and/or leads that are coated with an anti-scarring agent or a composition that includes an anti-scarring agent. As an alternative to this, or in addition to this, a composition that includes an anti-scarring agent can be infiltrated into the tissue surrounding the gastric nerve where the lead will be implanted.

[0120] g) Cochlear Implants for the Treatment of Deafness

[0121] Neurostimulation is also used in the form of a cochlear implant that stimulates the auditory nerve for correcting sensorineural deafness. A sound processor captures sound from the environment and processes it into a digital signal that is transmitted via an antenna through the skin to the cochlear implant. The cochlear implant, which is surgically implanted in the cochlea adjacent to the auditory nerve, converts the digital information into electrical signals that are communicated to the auditory nerve via an electrode array. Effectively, the cochlear implant serves to bypass the nonfunctional cochlear transducers and directly depolarize afferent auditory nerve fibers. This stimulates the nerve to send signals to the auditory center in the brain and allows the patient to "hear" the sounds detected by the sound processor. The treatment is used for adults with 70 dB or greater hearing loss (and able to understand up to 50% of words in a sentence using a hearing aid) or children 12 months or older with 90 dB hearing loss in both ears.

[0122] Although many implantations are performed without incident, approximately 12-15% of patients experience some complications. Histologic assessment of cochlear implants has revealed that several forms of injury and scarring can occur. Surgical trauma can induce cochlear fibrosis, cochlear neossification and injury to the membranous cochlea (including loss of the sensorineural elements). A foreign body reaction along the implant and the electrode can produce a fibrous tissue response along the electrode array that has been associated with implant failure. Coating the implant and/or the electrode with an anti-scarring composition may help reduce the incidence of failure. As an alternative, or in addition to this, fibrosis may be reduced or prevented by the infiltration of an anti-scarring agent into the tissue (the scala tympani) where the electrodes contact the auditory nerve fibers.

[0123] A variety of suitable cochlear implant systems or "bionic ears" have been described for use in association with this invention. For example, the neurostimulator may be composed of a plurality of transducer elements which detect vibrations and then generates a stimulus signal to a corresponding neuron connected to the cranial nerve. See e.g., U.S. Pat. No. 5,061,282. The neurostimulator may be a cochlear implant having a sound-to-electrical stimulation encoder, a body implantable receiver-stimulator and electrodes, which emit pulses based on received electrical signals. See e.g., U.S. Pat. No. 4,532,930. The neurostimulator may be an intra-cochlear apparatus that is composed of a transducer that converts an audio signal into an electrical signal and an electrode array which electrically stimulates predetermined locations of the auditory nerve. See e.g., U.S. Pat. No. 4,400,590. The neurostimulator may be a stimulus generator for applying electrical stimuli to any branch of the 8^{th} nerve in a generally constant rate independent of audio modulation, such that it is perceived as active silence. See e.g., U.S. Pat. No. 6,175,767. The neurostimulator may be a subcranially implanted electromechanical system that has an input transducer and an output stimulator that converts a mechanical sound vibration into an electrical signal. See e.g., U.S. Pat. No. 6,235,056. The neurostimulator may be a cochlear implant that has a rechargeable battery housed within the implant for storing and providing electrical power. See e.g., U.S. Pat. No. 6,067,474. Other neurostimulators that are used as cochlear implants are described in, e.g., U.S. Pat. Nos. 6,358,281; 6,308,101 and 5,603,726.

[0124] Several commercially available devices are available for the treatment of patients with significant sensorineural hearing loss and are suitable for use with the present invention. For example, the HIRESOLUTION Bionic Ear System (Boston Scientific Corp., Nattick, Mass.) consists of the HIRES AURIA Processor which processes sound and sends a digital signal to the HIRES 90K Implant that has

been surgically implanted in the inner ear. See e.g., U.S. Pat. Nos. 6,636,768; 6,309,410 and 6,259,951. The electrode array that transmits the impulses generated by the HIRES 90K Implant to the nerve may benefit from an anti-scarring coating and/or the infiltration of an anti-scarring agent into the region around the electrode-nerve interface. The PULSARci cochlear implant (MED-EL GMBH, Innsbruck, Austria, see e.g., U.S. Pat. Nos. 6,556,870 and 6,231,604) and the NUCLEUS 3 cochlear implant system (Cochlear Corp., Lane Cove, Australia, see e.g., U.S. Pat. Nos. 6,807,445; 6,788,790; 6,554,762; 6,537,200 and 6,394,947) are other commercial examples of cochlear implants whose electrodes are suitable for coating with an anti-scarring composition (or infiltration of an anti-scarring agent into the region around the electrode-nerve interface) under the present invention.

[0125] Regardless of the specific design features, for cochlear implants to be effective in sensorineural deafness, the electrode arrays must be accurately positioned adjacent to the afferent auditory nerve fibers. If excessive scar tissue growth or extracellular matrix deposition occurs around the leads, efficacy can be compromised. Cochlear implants that release a therapeutic agent able to reduce scarring at the electrode-tissue interface can increase the efficiency of impulse transmission and increase the duration that these devices function clinically. In one aspect, the device includes cochlear implants and/or leads that are coated with an anti-scarring agent or a composition that includes an anti-scarring agent. As an alternative to this, or in addition to this, a composition that includes an anti-scarring agent can be infiltrated into the cochlear tissue surrounding the lead.

[0126] h) Electrical Stimulation to Promote Bone Growth

[0127] In another aspect, electrical stimulation can be used to stimulate bone growth. For example, the stimulation device may be an electrode and generator having a strain response piezoelectric material which responds to strain by generating a charge to enhance the anchoring of an implanted bone prosthesis to the natural bone. See e.g., U.S. Pat. No. 6,143,035. If excessive scar tissue growth or extracellular matrix deposition occurs around the leads, efficacy can be compromised. Electrical bone stimulation devices that release a therapeutic agent able to reduce scarring at the electrode-tissue interface can increase the efficiency of impulse transmission and increase the duration that these devices function clinically. In one aspect, the device includes bone stimulation devices and/or leads that are coated with an anti-scarring agent or a composition that includes an anti-scarring agent. As an alternative to this, or in addition to this, a composition that includes an anti-scarring agent can be infiltrated into the bone tissue surrounding the electrical lead.

[0128] Although numerous neurostimulation devices have been described above, all possess similar design features and cause similar unwanted tissue reactions following implantation. It should be obvious to one of skill in the art that commercial neurostimulation devices not specifically sited above as well as next-generation and/or subsequently-developed commercial neurostimulation products are to be anticipated and are suitable for use under the present invention. The neurostimulation device, particularly the lead(s), must be positioned in a very precise manner to ensure that stimulation is delivered to the correct anatomical location in the nervous system. All, or parts, of a neurostimulation device can migrate following surgery, or excessive scar (or glial) tissue growth can occur around the implant, which can lead to a reduction in the performance of these devices. Neurostimulator devices that release a therapeutic agent for reducing scarring (or gliosis) at the electrode-tissue interface can be used to increase the efficacy and/or the duration of activity of the implant (particularly for fully-implanted, battery-powered devices). In one aspect, the present invention provides neurostimulator devices that include an anti-scarring (or anti-gliosis) agent or a composition that includes an anti-scarring (or anti-gliosis) agent. Numerous polymeric and non-polymeric delivery systems for use in neurostimulator devices have been described above. These compositions can further include one or more fibrosis-inhibiting (or gliosis-inhibiting) agents such that the overgrowth of granulation, fibrous, or gliotic tissue is inhibited or reduced.

[0129] Methods for incorporating fibrosis-inhibiting (or gliosis-inhibiting) compositions onto or into these neurostimulator devices include: (a) directly affixing to the device, lead and/or the electrode a fibrosis-inhibiting (or gliosis-inhibiting) composition (e.g., by either a spraying process or dipping process as described above, with or without a carrier), (b) directly incorporating into the device, lead and/or the electrode a fibrosis-inhibiting (or gliosis-inhibiting) composition (e.g., by either a spraying process or dipping process as described above, with or without a carrier (c) by coating the device, lead and/or the electrode with a substance such as a hydrogel which may in turn absorb the fibrosis-inhibiting (or gliosis-inhibiting) composition, (d) by interweaving fibrosis-inhibiting (or gliosis-inhibiting) composition coated thread (or the polymer itself formed into a thread) into the device, lead and/or electrode structure, (e) by inserting the device, lead and/or the electrode into a sleeve or mesh which is comprised of, or coated with, a fibrosis-inhibiting (or gliosis-inhibiting) composition, (f) constructing the device, lead and/or the electrode itself (or a portion of the device and/or the electrode) with a fibrosis-inhibiting (or gliosis-inhibiting) composition, or (g) by covalently binding the fibrosis-inhibiting (or gliosis-inhibiting) agent directly to the device, lead and/or electrode surface or to a linker (small molecule or polymer) that is coated or attached to the device surface. Each of these methods illustrates an approach for combining an electrical device with a fibrosis-inhibiting (also referred to herein as an anti-scarring) or gliosis-inhibiting agent according to the present invention.

[0130] For these devices, leads and electrodes, the coating process can be performed in such a manner as to: (a) coat the non-electrode portions of the lead or device; (b) coat the electrode portion of the lead; or (c) coat all or parts of the entire device with the fibrosis-inhibiting (or gliosis-inhibiting) composition. In addition to, or alternatively, the fibrosis-inhibiting (or gliosis-inhibiting) agent can be mixed with the materials that are used to make the device, lead and/or electrode such that the fibrosis-inhibiting agent is incorporated into the final product. In these manners, a medical device may be prepared which has a coating, where the coating is, e.g., uniform, non-uniform, continuous, discontinuous, or patterned.

[0131] In another aspect, a neurostimulation device may include a plurality of reservoirs within its structure, each reservoir configured to house and protect a therapeutic drug.

The reservoirs may be formed from divets in the device surface or micropores or channels in the device body. In one aspect, the reservoirs are formed from voids in the structure of the device. The reservoirs may house a single type of drug or more than one type of drug. The drug(s) may be formulated with a carrier (e.g., a polymeric or non-polymeric material) that is loaded into the reservoirs. The filled reservoir can function as a drug delivery depot which can release drug over a period of time dependent on the release kinetics of the drug from the carrier. In certain embodiments, the reservoir may be loaded with a plurality of layers. Each layer may include a different drug having a particular amount (dose) of drug, and each layer may have a different composition to further tailor the amount of drug that is released from the substrate. The multi-layered carrier may further include a barrier layer that prevents release of the drug(s). The barrier layer can be used, for example, to control the direction that the drug elutes from the void. Thus, the coating of the medical device may directly contact the electrical device, or it may indirectly contact the electrical device when there is something, e.g., a polymer layer, that is interposed between the electrical device and the coating that contains the fibrosis-inhibiting agent.

[0132] In addition to, or as an alternative to incorporating a fibrosis-inhibiting (or gliosis-inhibiting) agent onto or into the neurostimulation device, the fibrosis-inhibiting (or gliosis-inhibiting) agent can be applied directly or indirectly to the tissue adjacent to the neurostimulator device (preferably near the electrode-tissue interface). This can be accomplished by applying the fibrosis-inhibiting (or gliosis inhibiting) agent, with or without a polymeric, non-polymeric, or secondary carrier: (a) to the lead and/or electrode surface (e.g., as an injectable, paste, gel or mesh) during the implantation procedure); (b) to the surface of the tissue (e.g., as an injectable, paste, gel, in situ forming gel or mesh) prior to, immediately prior to, or during, implantation of the neurostimulation device, lead and/or electrode; (c) to the surface of the lead and/or electrode and/or the tissue surrounding the implanted lead and/or electrode (e.g., as an injectable, paste, gel, in situ forming gel or mesh) immediately after to the implantation of the neurostimulation device, lead and/or electrode; (d) by topical application of the anti-fibrosis (or gliosis) agent into the anatomical space where the neurostimulation device, lead and/or electrode will be placed (particularly useful for this embodiment is the use of polymeric carriers which release the fibrosis-inhibiting agent over a period ranging from several hours to several weeks—fluids, suspensions, emulsions, microemulsions, microspheres, pastes, gels, microparticulates, sprays, aerosols, solid implants and other formulations which release the agent can be delivered into the region where the device will be inserted); (e) via percutaneous injection into the tissue surrounding the device, lead and/or electrode as a solution as an infusate or as a sustained release preparation; (f) by any combination of the aforementioned methods. Combination therapies (i.e., combinations of therapeutic agents and combinations with antithrombotic and/or antiplatelet agents) can also be used.

[0133] It should be noted that certain polymeric carriers themselves can help prevent the formation of fibrous or gliotic tissue around the neuroimplant. These carriers (to be described shortly) are particularly useful for the practice of this embodiment, either alone, or in combination with a fibrosis (or gliosis) inhibiting composition. The following polymeric carriers can be infiltrated (as described in the previous paragraph) into the vicinity of the electrode-tissue interface and include: (a) sprayable collagen-containing formulations such as COSTASIS and crosslinked derivatized poly(ethylene glycol) collagen compositions (described, e.g., in U.S. Pat. Nos. 5,874,500 and 5,565,519 and referred to herein as "CT3" (both from Angiotech Pharmaceuticals, Inc., Canada), either alone, or loaded with a fibrosis-inhibiting (or gliosis-inhibiting) agent, applied to the implantation site (or the implant/device surface); (b) sprayable PEG-containing formulations such as COSEAL (Angiotech Pharmaceuticals, Inc.), FOCALSEAL (Genzyme Corporation, Cambridge, Mass.), SPRAYGEL or DURASEAL (both from Confluent Surgical, Inc., Boston, Mass.), either alone, or loaded with a fibrosis-inhibiting (or gliosis-inhibiting) agent, applied to the implantation site (or the implant/device surface); (c) fibrinogen-containing formulations such as FLOSEAL or TISSEAL (both from Baxter Healthcare Corporation, Fremont, Calif.), either alone, or loaded with a fibrosis-inhibiting (or gliosis-inhibiting) agent, applied to the implantation site (or the implant/device surface); (d) hyaluronic acid-containing formulations such as RESTYLANE or PERLANE (both from Q-Med AB, Sweden), HYLAFORM (Inamed Corporation, Santa Barbara, Calif.), SYNVISC (Biomatrix, Inc., Ridgefield, N.J.), SEPRAFILM or SEPRACOAT (both from Genzyme Corporation), loaded with a fibrosis-inhibiting (or gliosis-inhibiting) agent applied to the implantation site (or the implant/device surface); (e) polymeric gels for surgical implantation such as REPEL (Life Medical Sciences, Inc., Princeton, N.J.) or FLOWGEL (Baxter Healthcare Corporation) loaded with a fibrosis-inhibiting (or gliosis-inhibiting) agent applied to the implantation site (or the implant/device surface); (f) orthopedic "cements" used to hold prostheses and tissues in place loaded with a fibrosis-inhibiting (or gliosis-inhibiting) agent applied to the implantation site (or the implant/device surface), such as OSTEOBOND (Zimmer, Inc., Warsaw, Ind.), low viscosity cement (LVC); Wright Medical Technology, Inc., Arlington, Tenn.), SIMPLEX P (Stryker Corporation, Kalamazoo, Mich.), PALACOS (Smith & Nephew Corporation, United Kingdom), and ENDURANCE (Johnson & Johnson, Inc., New Brunswick, N.J.); (g) surgical adhesives containing cyanoacrylates such as DERMABOND (Johnson & Johnson, Inc.), INDERMIL (U.S. Surgical Company, Norwalk, Conn.), GLUSTITCH (Blacklock Medical Products Inc., Canada), TISSUEMEND (Veterinary Products Laboratories, Phoenix, Ariz.), VETBOND (3M Company, St. Paul, Minn.), HISTOACRYL BLUE (Davis & Geck, St. Louis, Mo.) and ORABASE SOOTHE-N-SEAL LIQUID PROTECTANT (Colgate-Palmolive Company, New York, N.Y.), either alone, or loaded with a fibrosis-inhibiting (or gliosis-inhibiting) agent, applied to the implantation site (or the implant/device surface); (h) implants containing hydroxyapatite [or synthetic bone material such as calcium sulfate, VITOSS and CORTOSS (both from Orthovita, Inc., Malvern, Pa.) loaded with a fibrosis-inhibiting (or gliosis-inhibiting) agent applied to the implantation site (or the implant/device surface); (i) other biocompatible tissue fillers loaded with a fibrosis-inhibiting (or gliosis-inhibiting) agent, such as those made by BioCure, Inc. (Norcross, Ga.), 3M Company (St. Paul, Minn.) and Neomend, Inc. (Sunnyvale, Calif.), applied to the implantation site (or the implant/device surface); (j) polysaccharide gels such as the ADCON series of gels

(available from Gliatech, Inc., Cleveland, Ohio) either alone, or loaded with a fibrosis-inhibiting (or gliosis-inhibiting) agent, applied to the implantation site (or the implant/device surface); and/or (k) films, sponges or meshes such as INTERCEED (Gynecare Worldwide, a division of Ethicon, Inc., Somerville, N.J.), VICRYL mesh (Ethicon, Inc.), and GELFOAM (Pfizer, Inc., New York, N.Y.) loaded with a fibrosis-inhibiting (or gliosis-inhibiting) agent applied to the implantation site (or the implant/device surface).

[0134] A preferred polymeric matrix which can be used to help prevent the formation of fibrous or gliotic tissue around the neuroimplant, either alone or in combination with a fibrosis (or gliosis) inhibiting agent/composition, is formed from reactants comprising either one or both of pentaerythritol poly(ethylene glycol)ether tetra-sulfhydryl] (4-armed thiol PEG, which includes structures having a linking group(s) between a sulfhydryl group(s) and the terminus of the polyethylene glycol backbone) and pentaerythritol poly-(ethylene glycol)ether tetra-succinimidyl glutarate] (4-armed NHS PEG, which again includes structures having a linking group(s) between a NHS group(s) and the terminus of the polyethylene glycol backbone) as reactive reagents. Another preferred composition comprises either one or both of pentaerythritol poly(ethylene glycol)ether tetra-amino] (4-armed amino PEG, which includes structures having a linking group(s) between an amino group(s) and the terminus of the polyethylene glycol backbone) and pentaerythritol poly(ethylene glycol)ether tetra-succinimidyl glutarate] (4-armed NHS PEG, which again includes structures having a linking group(s) between a NHS group(s) and the terminus of the polyethylene glycol backbone) as reactive reagents. Chemical structures for these reactants are shown in, e.g., U.S. Pat. No. 5,874,500. Optionally, collagen or a collagen derivative (e.g., methylated collagen) is added to the poly-(ethylene glycol)-containing reactant(s) to form a preferred crosslinked matrix that can serve as a polymeric carrier for a therapeutic agent or a stand-alone composition to help prevent the formation of fibrous or gliotic tissue around the neuroimplant.

[0135] It should be apparent to one of skill in the art that potentially any anti-scarring (or anti-gliotic) agent described above may be utilized alone, or in combination, in the practice of this embodiment. As neurostimulator devices are made in a variety of configurations and sizes, the exact dose administered will vary with device size, surface area and design. However, certain principles can be applied in the application of this art. Drug dose can be calculated as a function of dose per unit area (of the portion of the device being coated), total drug dose administered can be measured and appropriate surface concentrations of active drug can be determined. Regardless of the method of application of the drug to the device (i.e., as a coating or infiltrated into the surrounding tissue), the fibrosis-inhibiting (or gliosis-inhibiting) agents, used alone or in combination, may be administered under the following dosing guidelines:

[0136] Drugs and dosage: Exemplary therapeutic agents that may be used include, but are not limited to: antimicrotubule agents including taxanes (e.g., paclitaxel and docetaxel), other microtubule stabilizing agents, mycophenolic acid, rapamycin and vinca alkaloids (e.g., vinblastine and vincristine sulfate). Drugs are to be used at concentrations that range from a single systemic dose (e.g., the dose used in oral or i.v. administration) to a fraction of a single systemic dose (e.g., 50%, 10%, 5%, or even less than 1% of the concentration typically used in a single systemic dose application). Preferably, the drug is released in effective concentrations for a period ranging from 1-90 days. Anti-microtubule agents including taxanes, such as paclitaxel and analogues and derivatives (e.g., docetaxel) thereof, and vinca alkaloids, including vinblastine and vincristine sulfate and analogues and derivatives thereof, should be used under the following parameters: total dose not to exceed 10 mg (range of 0.1 μg to 10 mg); preferred total dose 1 μg to 3 mg. Dose per unit area of the device of 0.05 μg-10 μg per mm^{-1}; preferred dose/unit area of 0.20 $\mu g/mm^2$-5 $\mu g/mm^2$. Minimum concentration of 10^{-9}-10^{-4} M of drug is to be maintained on the device surface. Immunomodulators including sirolimus and everolimus. Sirolimus (i.e., rapamycin, RAPAMUNE): Total dose not to exceed 10 mg (range of 0.1 μg to 10 mg); preferred 10 μg to 1 mg. The dose per unit area of 0.1 μg-100 μg per mm^2; preferred dose of 0.5 $\mu g/mm^2$-10 $\mu g/mm^2$. Minimum concentration of 10^{-8}-10^{-4} M is to be maintained on the device surface. Everolimus and derivatives and analogues thereof: Total dose should not exceed 10 mg (range of 0.1 μg to 10 mg); preferred 10 μg to 1 mg. The dose per unit area of 0.1 μg-100 μg per mm^2 of surface area; preferred dose of 0.3 $\mu g/mm^2$-10 $\mu g/mm^2$. Minimum concentration of 10^{-8}-10^{-4} M of everolimus is to be maintained on the device surface. Inosine monophosphate dehydrogenase inhibitors (e.g., mycophenolic acid, 1-alpha-25 dihydroxy vitamin D_3) and analogues and derivatives thereof: total dose not to exceed 2000 mg (range of 10.0 μg to 2000 mg); preferred 10 μg to 300 mg. The dose per unit area of the device of 1.0 μg-1000 μg per mm^2; preferred dose of 2.5 $\mu g/mm^2$-500 $\mu g/mm^2$. Minimum concentration of 10^{-8}-10^{-3} M of mycophenolic acid is to be maintained on the device surface.

[0137] 2) Cardiac Rhythm Management (CRM) Devices

[0138] In another aspect, the electrical device may be a cardiac pacemaker device where a pulse generator delivers an electrical impulse to myocardial tissue (often specialized conduction fibres) via an implanted lead in order to regulate cardiac rhythm. Typically, electrical leads are composed of a connector assembly, a lead body (i.e., conductor) and an electrode. Electrical leads may be unipolar, in which they are adapted to provide effective therapy with only one electrode. Multi-polar leads are also available, including bipolar, tripolar and quadripolar leads. Electrical leads may also have insulating sheaths which may include polyurethane or silicone-rubber coatings. Representative examples of electrical leads include, without limitation, medical leads, cardiac leads, pacer leads, pacing leads, pacemaker leads, endocardial leads, endocardial pacing leads, cardioversion/defibrillator leads, cardioversion leads, epicardial leads, epicardial defibrillator leads, patch defibrillators, patch leads, electrical patch, transvenous leads, active fixation leads, passive fixation leads and sensing leads Representative examples of CRM devices that utilize electrical leads include: pacemakers, LVAD's, defibrillators, implantable sensors and other electrical cardiac stimulation devices.

[0139] There are numerous pacemaker devices where the occurrence of a fibrotic reaction will adversely affect the functioning of the device or cause damage to the myocardial tissue. Typically, fibrotic encapsulation of the pacemaker lead (or the growth of fibrous tissue between the lead and the target myocardial tissue) slows, impairs, or interrupts elec-

trical transmission of the impulse from the device to the myocardium. For example, fibrosis is often found at the electrode-myocardial interfaces in the heart, which may be attributed to electrical injury from focal points on the electrical lead. The fibrotic injury may extend into the tricuspid valve, which may lead to perforation. Fibrosis may lead to thrombosis of the subclavian vein; a condition which may be life-threatening. Electrical leads that release therapeutic agent for reducing scarring at the electrode-tissue interface may help prolong the clinical performance of these devices. Not only can fibrosis cause the device to function suboptimally or not at all, it can cause excessive drain on battery life as increased energy is required to overcome the electrical resistance imposed by the intervening scar tissue. Similarly, fibrotic encapsulation of the sensing components of a rate-responsive pacemaker (described below) can impair the ability of the pacemaker to identify and correct rhythm abnormalities leading to inappropriate pacing of the heart or the failure to function correctly when required.

[0140] Several different electrical pacing devices are used in the treatment of various cardiac rhythm abnormalities including pacemakers, implantable cardioverter defibrillators (ICD), left ventricular assist devices (LVAD), and vagus nerve stimulators (stimulates the fibers of the vagus nerve which in turn innervate the heart). The pulse generating portion of device sends electrical impulses via implanted leads to the muscle (myocardium) or conduction tissue of the heart to affect cardiac rhythm or contraction. Pacing can be directed to one or more chambers of the heart. Cardiac pacemakers may be used to block, mask, or stimulate electrical signals in the heart to treat dysfunctions, including, without limitation, atrial rhythm abnormalities, conduction abnormalities and ventricular rhythm abnormalities. ICDs are used to depolarize the ventricals and re-establish rhythm if a ventricular arrhythmia occurs (such as asystole or ventricular tachycardia) and LVADs are used to assist ventricular contraction in a failing heart.

[0141] Representative examples of patents which describe pacemakers and pacemaker leads include U.S. Pat. Nos. 4,662,382, 4,782,836, 4,856,521, 4,860,751, 5,101,824, 5,261,419, 5,284,491,6,055,454, 6,370,434, and 6,370,434. Representative examples of electrical leads include those found on a variety of cardiac devices, such as cardiac stimulators (see e.g., U.S. Pat. Nos. 6,584,351 and 6,115, 633), pacemakers (see e.g., U.S. Pat. Nos. 6,564,099; 6,246, 909 and 5,876,423), implantable cardioverter-defibrillators (ICDs), other defibrillator devices (see e.g., U.S. Pat. No. 6,327,499), defibrillator or demand pacer catheters (see e.g., U.S. Pat. No. 5,476,502) and Left Ventricular Assist Devices (see e.g., U.S. Pat. No. 5,503,615).

[0142] Cardiac rhythm devices, and in particular the lead(s) that deliver the electrical pulsation, must be positioned in a very precise manner to ensure that stimulation is delivered to the correct anatomical location in the heart. All, or parts, of a pacing device can migrate following surgery, or excessive scar tissue growth can occur around the lead, which can lead to a reduction in the performance of these devices (as described previously). Cardiac rhythm management devices that release a therapeutic agent for reducing scarring at the electrode-tissue interface can be used to increase the efficacy and/or the duration of activity (particularly for fully-implanted, battery-powered devices) of the implant. Accordingly, the present invention provides cardiac leads that are coated with an anti-scarring agent or a composition that includes an anti-scarring agent.

[0143] For greater clarity, several specific cardiac rhythm management devices and treatments will be described in greater detail including:

[0144] a) Cardiac Pacemakers

[0145] Cardiac rhythm abnormalities are extremely common in clinical practice and the incidence increases in frequency with both age and the presence of underlying coronary artery disease or myocardial infarction. A litany of arrythmias exists, but they are generally categorized into conditions where the heart beats too slowly (bradyarrythmias—such heart block, sinus node dysfunction) or too quickly (tachyarrhythmias—such as atrial fibrillation, WPW syndrome, ventricular fibrillation). A pacemaker functions by sending an electrical pulse (a pacing pulse) that travels via an electrical lead to the electrode (at the tip of the lead) which delivers an electrical impulse to the heart that initiates a heartbeat. The leads and electrodes can be located in one chamber (either the right atrium or the right ventricle—called single-chamber pacemakers) or there can be electrodes in both the right atrium and the right ventricle (called dual-chamber pacemakers). Electrical leads may be implanted on the exterior of the heart (e.g., epicardial leads) by a surgical procedure, or they can be connected to the endocardial surface of the heart via a catheter, guidewire or stylet. In some pacemakers, the device assumes the rhythm generating function of the heart and fires at a regular rate. In other pacemakers, the device merely augments the heart's own pacing function and acts "on demand" to provide pacing assistance as required (called "adaptive-rate" pacemakers); the pacemaker receives feedback on heart rhythm (and hence when to fire) from an electrode sensor located on the lead. Other pacemakers, called rate responsive pacemakers, have special sensors that detect changes in body activity (such as movement of the arms and legs, respiratory rate) and adjust pacing up or down accordingly.

[0146] Numerous pacemakers and pacemaker leads are suitable for use in this invention. For example, the pacing lead may have an increased resistance to fracture by being composed of an elongated coiled conductor mounted within a lumen of a lead body whereby it may be coupled electrically to a stranded conductor. See e.g., U.S. Pat. Nos. 6,061,598 and 6,018,683. The pacing lead may have a coiled conductor with an insulated sheath, which has a resistance to crush fatigue in the region between the rib and clavicle. See e.g., U.S. Pat. No. 5,800,496. The pacing lead may be expandable from a first, shorter configuration to a second, longer configuration by being composed of slideable inner and outer overlapping tubes containing a conductor. See e.g., U.S. Pat. No. 5,897,585. The pacing lead may have the means for temporarily making the first portion of the lead body stiffer by using a magnet-rheologic fluid in a cavity that stiffens when exposed to a magnetic field. See e.g., U.S. Pat. No. 5,800,497. The pacing lead may be a coil configuration composed of a plurality of wires or wire bundles made from a duplex titanium alloy. See e.g., U.S. Pat. No. 5,423,881. The pacing lead may be composed of a wire wound in a coil configuration with the wire composed of stainless steel having a composition of at least 22% nickel and 2% molybdenum. See e.g., U.S. Pat. No. 5,433,744. Other pacing leads are described in, e.g., U.S. Pat. Nos. 6,489,562; 6,289,251 and 5,957,967.

[0147] In another aspect, the electrical lead used in the practice of this invention may have an active fixation element for attachment to tissue. For example, the electrical lead may have a rigid fixation helix with microgrooves that are dimensioned to minimize the foreign body response following implantation. See e.g., U.S. Pat. No. 6,078,840. The electrical lead may have an electrode/anchoring portion with a dual tapered self-propelling spiral electrode for attachment to vessel wall. See e.g., U.S. Pat. No. 5,871,531. The electrical lead may have a rigid insulative electrode head carrying a helical electrode. See e.g., U.S. Pat. No. 6,038,463. The electrical lead may have an improved anchoring sleeve designed with an introducer sheath to minimize the flow of blood through the sheath during introduction. See e.g., U.S. Pat. No. 5,827,296. The electrical lead may be composed of an insulated electrical conductive portion and a lead-in securing section having a longitudinally rigid helical member which may be screwed into tissue. See e.g., U.S. Pat. No. 4,000,745.

[0148] Suitable leads for use in the practice of this invention also include multi-polar leads with multiple electrodes connected to the lead body. For example, the electrical lead may be a multi-electrode lead whereby the lead has two internal conductors and three electrodes with two electrodes coupled by a capacitor integral with the lead. See e.g., U.S. Pat. No. 5,824,029. The electrical lead may be a lead body with two straight sections and a bent third section with associated conductors and electrodes whereby the electrodes are bipolar. See e.g., U.S. Pat. No. 5,995,876. In another aspect, the electrical lead may be implanted by using a catheter, guidewire or stylet. For example, the electrical lead may be composed of an elongated insulative lead body having a lumen with a conductor mounted within the lead body and a resilient seal having an expandable portion through which a guidewire may pass. See e.g., U.S. Pat. No. 6,192,280.

[0149] Commercially available pacemakers suitable for the practice of the invention include the KAPPA SR 400 Series single-chamber rate-responsive pacemaker system, the KAPPA DR 400 Series dual-chamber rate-responsive pacemaker system, the KAPPA 900 and 700 Series single-chamber rate-responsive pacemaker system, and the KAPPA 900 and 700 Series dual-chamber rate-responsive pacemaker system by Medtronic, Inc. Medtronic pacemaker systems utilize a variety leads including the CAPSURE Z Novus, CAPSUREFIX Novus, CAPSUREFIX, CAPSURE SP Novus, CAPSURE SP, CAPSURE EPI and the CAPSURE VDD which may be suitable for coating with a fibrosis-inhibiting agent. Pacemaker systems and associated leads that are made by Medtronic are described in, e.g., U.S. Pat. Nos. 6,741,893; 5,480,441; 5,411,545; 5,324,310; 5,265,602; 5,265,601; 5,241,957 and 5,222,506. Medtronic also makes a variety of steroid-eluting leads including those described in, e.g., U.S. Pat. Nos. 5,987,746; 6,363,287; 5,800,470; 5,489,294; 5,282,844 and 5,092,332. The INSIGNIA single-chamber and dual-chamber system, PULSAR MAX II DR dual-chamber adaptive-rate pacemaker, PULSAR MAX II SR single-chamber adaptive-rate pacemaker, DISCOVERY II DR dual-chamber adaptive-rate pacemaker, DISCOVERY II SR single-chamber adaptive-rate pacemaker, DISCOVERY II DDD dual-chamber pacemaker, and the DISCOVERY II SSI dingle-chamber pacemaker systems made by Guidant Corp. (Indianapolis, Ind.) are also suitable pacemaker systems for the practice of this invention. Once again, the leads from the Guidant pacemaker systems may be suitable for coating with a fibrosis-inhibiting agent. Pacemaker systems and associated leads that are made by Guidant are described in, e.g., U.S. Pat. Nos. 6,473,648; 6,345,204; 6,321,122; 6,152,954; 5,769,881; 5,284,136; 5,086,773 and 5,036,849. The AFFINITY DR, AFFINITY VDR, AFFINITY SR, AFFINITY DC, ENTITY, IDENTITY, IDENTITY ADX, INTEGRITY, INTEGRITY μDR, INTEGRITY ADx, MICRONY, REGENCY, TRILOGY, and VERITY ADx, pacemaker systems and leads from St. Jude Medical, Inc. (St. Paul, Minn.) may also be suitable for use with a fibrosis-inhibiting coating to improve electrical transmission and sensing by the pacemaker leads. Pacemaker systems and associated leads that are made by St. Jude Medical are described in, e.g., U.S. Pat. Nos. 6,763,266; 6,760,619; 6,535,762; 6,246,909; 6,198,973; 6,183,305; 5,800,468 and 5,716,390. Alternatively, the fibrosis-inhibiting agent may be infiltrated into the region around the electrode-cardiac muscle interface under the present invention. It should be obvious to one of skill in the art that commercial pacemakers not specifically sited as well as next-generation and/or subsequently developed commercial pacemaker products are to be anticipated and are suitable for use under the present invention.

[0150] Regardless of the specific design features, for pacemakers to be effective in the management of cardiac rhythm disorders, the leads must be accurately positioned adjacent to the targeted cardiac muscle tissue. If excessive scar tissue growth or extracellular matrix deposition occurs around the leads, efficacy can be compromised. Pacemaker leads that release a therapeutic agent able to reduce scarring at the electrode-tissue and/or sensor-tissue interface, can increase the efficiency of impulse transmission and rhythm sensing, thereby increasing efficacy and battery longevity. In one aspect, the device includes pacemaker leads that are coated with an anti-scarring agent or a composition that includes an anti-scarring agent. As an alternative to this, or in addition to this, a composition that includes an anti-scarring agent can be infiltrated into the myocardial tissue surrounding the lead.

[0151] b) Implantable Cardioverter Defibrillator (ICD) Systems

[0152] Implantable cardioverter defibrillator (ICD) systems are similar to pacemakers (and many include a pacemaker system), but are used for the treatment of tachyarrhythmias such as ventricular tachycardia or ventricular fibrillation. An ICD consists of a mini-computer powered by a battery which is connected to a capacitor to helps the ICD charge and store enough energy to deliver therapy when needed. The ICD uses sensors to monitor the activity of the heart and the computer analysizes the data to determine when and if an arrhythmia is present. An ICD lead, which is inserted via a vein (called "transvenous" leads; in some systems the lead is implanted surgically—called an epicardial lead—and sewn onto the surface of the heart), connects into the pacing/computer unit. The lead, which is usually placed in the right ventricle, consists of an insulated wire and an electrode tip that contains a sensing component (to detect cardiac rhythm) and a shocking coil. A single-chamber ICD has one lead placed in the ventricle which defibrillates and paces the ventricle, while a dual-chamber ICD defibrillates the ventricle and paces the atrium and the ventricle. In some cases, an additional lead is required and

is placed under the skin next to the rib cage or on the surface of the heart. In patients who require tachyarrhythmia management of the ventricle and atrium, a second coil is placed in the atrium to treat atrial tachycardia, atrial fibrillation and other arrhythmias. If a tachyarrhythmia is detected, a pulse is generated and propagated via the lead to the shocking coil which delivers a charge sufficient to depolarize the muscle and cardiovert or defibrillate the heart.

[0153] Several ICD systems have been described and are suitable for use in the practice of this invention. Representative examples of ICD's and associated components are described in U.S. Pat. Nos. 3,614,954, 3,614,955, 4,375,817, 5,314,430, 5,405,363, 5,607,385, 5,697,953, 5,776,165, 6,067,471, 6,169,923, and 6,152,955. Several ICD leads are suitable for use in the practice of this invention. For example, the defibrillator lead may be a linear assembly of sensors and coils formed into a loop which includes a conductor system for coupling the loop system to a pulse generator. See e.g., U.S. Pat. No. 5,897,586. The defibrillator lead may have an elongated lead body with an elongated electrode extending from the lead body, such that insulative tubular sheaths are slideably mounted around the electrode. See e.g., U.S. Pat. No. 5,919,222. The defibrillator lead may be a temporary lead with a mounting pad and a temporarily attached conductor with an insulative sleeve whereby a plurality of wire electrodes are mounted. See e.g., U.S. Pat. No. 5,849,033. Other defibrillator leads are described in, e.g., U.S. Pat. No. 6,052,625. In another aspect, the electrical lead may be adapted to be used for pacing, defibrillating or both applications. For example, the electrical lead may be an electrically insulated, elongated, lead body sheath enclosing a plurality of lead conductors that are separated from contacting one another. See e.g., U.S. Pat. No. 6,434,430. The electrical lead may be composed of an inner lumen adapted to receive a stiffening member (e.g., guide wire) that delivers fluoro-visible media. See e.g., U.S. Pat. No. 6,567,704. The electrical lead may be a catheter composed of an elongated, flexible, electrically nonconductive probe contained within an electrically conductive pathway that transmits electrical signals, including a defibrillation pulse and a pacer pulse, depending on the need that is sensed by a governing element. See e.g., U.S. Pat. No. 5,476,502. The electrical lead may have a low electrical resistance and good mechanical resistance to cyclical stresses by being composed of a conductive wire core formed into a helical coil covered by a layer of electrically conductive material and an electrically insulating sheath covering. See e.g., U.S. Pat. No. 5,330,521. Other electrical leads that may be adapted for use in pacing and/or defibrillating applications are described in, e.g., U.S. Pat. No. 6,556,873.

[0154] Commercially available ICDs suitable for the practice of the invention include the GEM III DR dual-chamber ICD, GEM III VR ICD, GEM II ICD, GEM ICD, GEM III AT atrial and ventricular arrhythmia ICD, JEWEL AF dual-chamber ICD, MICRO JEWEL ICD, MICRO JEWEL II ICD, JEWEL Plus ICD, JEWEL ICD, JEWEL ACTIVE CAN ICD, JEWEL PLUS ACTIVE CAN ICD, MAXIMO DR ICD, MAXIMO VR ICD, MARQUIS DR ICD, MARQUIS VR system, and the INTRINSIC dual-chamber ICD by Medtronic, Inc. Medtronic ICD systems utilize a variety leads including the SPRINT FIDELIS, SPRINT QUATRO SECURE steroid-eluting bipolar lead, Subcutaneous Lead System Model 6996SQ subcutaneous lead, TRANSVENE 6937A transvenous lead, and the 6492 Unipolar Atrial Pacing Lead which may be suitable for coating with a fibrosis-inhibiting agent. ICD systems and associated leads that are made by Medtronic are described in, e.g., U.S. Pat. Nos. 6,038,472; 5,849,031; 5,439,484; 5,314,430; 5,165,403; 5,099,838 and 4,708,145. The VITALITY 2 DR dual-chamber ICD, VITALITY 2 VR single-chamber ICD, VITALITY AVT dual-chamber ICD, VITALITY DS dual-chamber ICD, VITALITY DS VR single-chamber ICD, VITALITY EL dual-chamber ICD, VENTAK PRIZM 2 DR dual-chamber ICD, and VENTAK PRIZM 2 VR single-chamber ICD systems made by Guidant Corp. are also suitable ICD systems for the practice of this invention. Once again, the leads from the Guidant ICD systems may be suitable for coating with a fibrosis-inhibiting agent. Guidant sells the FLEXTEND Bipolar Leads, EASYTRAK Lead System, FINELINE Leads, and ENDOTAK RELIANCE ICD Leads. ICD systems and associated leads that are made by Guidant are described in, e.g., U.S. Pat. Nos. 6,574,505; 6,018,681; 5,697,954; 5,620,451; 5,433,729; 5,350,404; 5,342,407; 5,304,139 and 5,282,837. Biotronik, Inc. (Germany) sells the POLYROX Endocardial Leads, KENTROX SL Quadripolar ICD Leads, AROX Bipolar Leads, and MAPOX Bipolar Epicardial Leads (see e.g., U.S. Pat. Nos. 6,449,506; 6,421,567; 6,418,348; 6,236,893 and 5,632,770). The CONTOUR MD ICD, PHOTON p DR ICD, PHOTON p VR ICD, ATLAS+HF ICD, EPIC HF ICD, EPIC+HF ICD systems and leads from St. Jude Medical may also be suitable for use with a fibrosis-inhibiting coating to improve electrical transmission and sensing by the ICD leads (see e.g., U.S. Pat. Nos. 5,944,746; 5,722,994; 5,662,697; 5,542,173; 5,456,706 and 5,330,523). Alternatively, the fibrosis-inhibiting agent may be infiltrated into the region around the electrode-cardiac muscle interface under the present invention. It should be obvious to one of skill in the art that commercial ICDs not specifically sited as well as next-generation and/or subsequently developed commercial ICD products are to be anticipated and are suitable for use under the present invention.

[0155] Regardless of the specific design features, for ICDs to be effective in the management of cardiac rhythm disorders, the leads must be accurately positioned adjacent to the targeted cardiac muscle tissue. If excessive scar tissue growth or extracellular matrix deposition occurs around the leads, efficacy can be compromised. ICD leads that release a therapeutic agent able to reduce scarring at the electrode-tissue and/or sensor-tissue interface, can increase the efficiency of impulse transmission and rhythm sensing, thereby increasing efficacy, preventing inappropriate cardioversion, and improving battery longevity. In one aspect, the device includes ICD leads that are coated with an anti-scarring agent or a composition that includes an anti-scarring agent. As an alternative to this, or in addition to this, a composition that includes an anti-scarring agent can be infiltrated into the myocardial tissue surrounding the lead.

[0156] c) Vagus Nerve Stimulation for the Treatment of Arrhythmia

[0157] In another aspect, a neurostimulation device may be used to stimulate the vagus nerve and affect the rhythm of the heart. Since the vagus nerve provides innervation to the heart, including the conduction system (including the SA node), stimulation of the vagus nerve may be used to treat conditions such as supraventricular arrhythmias, angina

pectoris, atrial tachycardia, atrial flutter, atrial fibrillation and other arrhythmias that result in low cardiac output.

[0158] As described above, in VNS a bipolar electrical lead is surgically implanted such that it transmits electrical stimulation from the pulse generator to the left vagus nerve in the neck. The pulse generator is an implanted, lithium carbon monofluoride battery-powered device that delivers a precise pattern of stimulation to the vagus nerve. The pulse generator can be programmed (using a programming wand) by the cardiologist to treat a specific arrhythmia.

[0159] Products such as these have been described, for example, in U.S. Pat. Nos. 6,597,953 and 6,615,085. For example, the neurostimulator may be a vagal-stimulation apparatus which generates pulses at a frequency that varies automatically based on the excitation rates of the vagus nerve. See e.g., U.S. Pat. Nos. 5,916,239 and 5,690,681. The neurostimulator may be an apparatus that detects characteristics of tachycardia based on an electrogram and delivers a preset electrical stimulation to the nervous system to depress the heart rate. See e.g., U.S. Pat. No. 5,330,507. The neurostimulator may be an implantable heart stimulation system composed of two sensors, one for atrial signals and one for ventricular signals, and a pulse generator and control unit, to ensure sympatho-vagal stimulation balance. See e.g., U.S. Pat. No. 6,477,418. The neurostimulator may be a device that applies electrical pulses to the vagus nerve at a programmable frequency that is adjusted to maintain a lower heart rate. See e.g., U.S. Pat. No. 6,473,644. The neurostimulator may provide electrical stimulation to the vagus nerve to induce changes to electroencephalogram readings as a treatment for epilepsy, while controlling the operation of the heart within normal parameters. See e.g., U.S. Pat. No. 6,587,727.

[0160] A commercial example of a VNS system is the product produced by Cyberonics Inc. that consists of the Model 300 and Model 302 leads, the Model 101 and Model 102R pulse generators, the Model 201 programming wand and Model 250 programming software, and the Model 220 magnets. These products manufactured by Cyberonics, Inc. may be described, for example, in U.S. Pat. Nos. 5,928,272; 5,540,730 and 5,299,569.

[0161] Regardless of the specific design features, for vagal nerve stimulation to be effective in arrhythmias, the leads must be accurately positioned adjacent to the left vagus nerve. If excessive scar tissue growth or extracellular matrix deposition occurs around the VNS leads, this can reduce the efficacy of the device. VNS devices that release a therapeutic agent able to reducing scarring at the electrode-tissue interface can increase the efficiency of impulse transmission and increase the duration that these devices function clinically. In one aspect, the device includes VNS devices and/or leads that are coated with an anti-scarring agent or a composition that includes an anti-scarring agent. As an alternative to this, or in addition to this, a composition that includes an anti-scarring agent can be infiltrated into the tissue surrounding the vagus nerve where the lead will be implanted.

[0162] Although numerous cardiac rhythm management (CRM) devices have been described above, all possess similar design features and cause similar unwanted fibrous tissue reactions following implantation. The CRM device, particularly the lead(s), must be positioned in a very precise manner to ensure that stimulation is delivered to the correct anatomical location within the atrium and/or ventricle. All, or parts, of a CRM device can migrate following surgery, or excessive scar tissue growth can occur around the implant, which can lead to a reduction in the performance of these devices. CRM devices that release a therapeutic agent for reducing scarring at the electrode-tissue interface can be used to increase the efficacy and/or the duration of activity of the implant (particularly for fully-implanted, battery-powered devices). In one aspect, the present invention provides CRM devices that include a fibrosis-inhibiting agent or a composition that includes a fibrosis-inhibiting agent. Numerous polymeric and non-polymeric delivery systems for use in CRM devices have been described above. These compositions can further include one or more fibrosis-inhibiting agents such that the overgrowth of granulation or fibrous tissue is inhibited or reduced.

[0163] Methods for incorporating fibrosis-inhibiting compositions onto or into CRM devices include: (a) directly affixing to the CRM device, lead and/or electrode a fibrosis-inhibiting composition (e.g., by either a spraying process or dipping process as described above, with or without a carrier), (b) directly incorporating into the CRM device, lead and/or electrode a fibrosis-inhibiting composition (e.g., by either a spraying process or dipping process as described above, with or without a carrier (c) by coating the CRM device, lead and/or electrode with a substance such as a hydrogel which will in turn absorb the fibrosis-inhibiting composition, (d) by interweaving fibrosis-inhibiting composition coated thread (or the polymer itself formed into a thread) into the device, lead and/or electrode structure, (e) by inserting the CRM device, lead and/or electrode into a sleeve or mesh which is comprised of, or coated with, a fibrosis-inhibiting composition, (f) constructing the CRM device, lead and/or electrode itself (or a portion of the lead and/or electrode) with a fibrosis-inhibiting composition, or (g) by covalently binding the fibrosis-inhibiting agent directly to the CRM device, lead and/or electrode surface, or to a linker (small molecule or polymer) that is coated or attached to the device, lead and/or electrode surface. Each of these methods illustrates an approach for combining an electrical device with a fibrosis-inhibiting (also referred to herein as an anti-scarring) or gliosis-inhibiting agent according to the present invention.

[0164] For CRM devices, leads and electrodes, the coating process can be performed in such a manner as to: (a) coat the non-electrode portions of the lead; (b) coat the electrode portion of the lead; or (c) coat all or parts of the entire device with the fibrosis-inhibiting composition. In addition to, or alternatively, the fibrosis-inhibiting agent can be mixed with the materials that are used to make the CRM device, lead and/or electrode such that the fibrosis-inhibiting agent is incorporated into the final product. In these manners, a medical device may be prepared which has a coating, where the coating is, e.g., uniform, non-uniform, continuous, discontinuous, or patterned.

[0165] In another aspect, a CRM device may include a plurality of reservoirs within its structure, each reservoir configured to house and protect a therapeutic drug. The reservoirs may be formed from divets in the device surface or micropores or channels in the device body. In one aspect, the reservoirs are formed from voids in the structure of the device. The reservoirs may house a single type of drug or more than one type of drug. The drug(s) may be formulated with a carrier (e.g., a polymeric or non-polymeric material) that is loaded into the reservoirs. The filled reservoir can function as a drug delivery depot which can release drug over a period of time dependent on the release kinetics of the drug from the carrier. In certain embodiments, the reservoir may be loaded with a plurality of layers. Each layer may

include a different drug having a particular amount (dose) of drug, and each layer may have a different composition to further tailor the amount of drug that is released from the substrate. The multi-layered carrier may further include a barrier layer that prevents release of the drug(s). The barrier layer can be used, for example, to control the direction that the drug elutes from the void. Thus, the coating of the medical device may directly contact the electrical device, or it may indirectly contact the electrical device when there is something, e.g., a polymer layer, that is interposed between the electrical device and the coating that contains the fibrosis-inhibiting agent.

[0166] In addition to, or as an alternative to incorporating a fibrosis-inhibiting agent onto, or into, the CRM device, the fibrosis-inhibiting agent can be applied directly or indirectly to the tissue adjacent to the CRM device (preferably near the electrode-tissue interface). This can be accomplished by applying the fibrosis-inhibiting agent, with or without a polymeric, non-polymeric, or secondary carrier: (a) to the lead and/or electrode surface (e.g., as an injectable, paste, gel, or mesh) during the implantation procedure; (b) to the surface of the tissue (e.g., as an injectable, paste, gel, in situ forming gel, or mesh) prior to, immediately prior to, or during, implantation of the CRM device and/or the lead; (c) to the surface of the CRM lead and/or electrode and/or to the tissue surrounding the implanted lead or electrode (e.g., as an injectable, paste, gel, in situ forming gel, or mesh) immediately after the implantation of the CRM device, lead and/or electrode; (d) by topical application of the anti-fibrosis agent into the anatomical space where the CRM device, lead and/or electrode will be placed (particularly useful for this embodiment is the use of polymeric carriers which release the fibrosis-inhibiting agent over a period ranging from several hours to several weeks—fluids, suspensions, emulsions, microemulsions, microspheres, pastes, gels, microparticulates, sprays, aerosols, solid implants and other formulations which release the agent can be delivered into the region where the CRM device, lead and/or electrode will be inserted); (e) via percutaneous injection into the tissue surrounding the CRM device, lead and/or electrode as a solution, as an infusate, or as a sustained release preparation; (f) by any combination of the aforementioned methods. Combination therapies (i.e., combinations of therapeutic agents and combinations with antithrombotic and/or antiplatelet agents) can also be used.

[0167] It should be noted that certain polymeric carriers themselves can help prevent the formation of fibrous tissue around the CRM lead and electrode. These carriers (to be described shortly) are particularly useful for the practice of this embodiment, either alone, or in combination with a fibrosis-inhibiting composition. The following polymeric carriers can be infiltrated (as described in the previous paragraph) into the vicinity of the CRM device, lead and/or electrode-tissue interface and include: (a) sprayable collagen-containing formulations such as COSTASIS and CT3, either alone, or loaded with a fibrosis-inhibiting agent, applied to the implantation site (or the implant/device surface); (b) sprayable PEG-containing formulations such as COSEAL, FOCALSEAL, SPRAYGEL or DURASEAL, either alone, or loaded with a fibrosis-inhibiting agent, applied to the implantation site (or the implant/device surface); (c) fibrinogen-containing formulations such as FLOSEAL or TISSEAL, either alone, or loaded with a fibrosis-inhibiting agent, applied to the implantation site (or the implant/device surface); (d) hyaluronic acid-containing formulations such as RESTYLANE, HYLAFORM, PERLANE, SYNVISC, SEPRAFILM, SEPRACOAT, loaded with a fibrosis-inhibiting agent applied to the implantation site (or the implant/device surface); (e) polymeric gels for surgical implantation such as REPEL or FLOWGEL loaded with a fibrosis-inhibiting agent applied to the implantation site (or the implant/device surface); (f) orthopedic "cements" used to hold prostheses and tissues in place loaded with a fibrosis-inhibiting agent applied to the implantation site (or the implant/device surface), such as OSTEOBOND, low viscosity cement (LVC), SIMPLEX P, PALACOS, and ENDURANCE; (g) surgical adhesives containing cyanoacrylates such as DERMABOND, INDERMIL, GLUSTITCH, TISSUMEND, VETBOND, HISTOACRYL BLUE and ORABASE SOOTHE-N-SEAL LIQUID PROTECTANT, either alone, or loaded with a fibrosis-inhibiting agent, applied to the implantation site (or the implant/device surface); (h) implants containing hydroxyapatite [or synthetic bone material such as calcium sulfate, VITOSS and CORTOSS (Orthovita)] loaded with a fibrosis-inhibiting agent applied to the implantation site (or the implant/device surface); (i) other biocompatible tissue fillers loaded with a fibrosis-inhibiting agent, such as those made by BioCure, Inc., 3M Company and Neomend, Inc., applied to the implantation site (or the implant/device surface); 0) polysaccharide gels such as the ADCON series of gels either alone, or loaded with a fibrosis-inhibiting agent, applied to the implantation site (or the implant/device surface); and/or (k) films, sponges or meshes such as INTERCEED, VICRYL mesh, and GELFOAM loaded with a fibrosis-inhibiting agent applied to the implantation site (or the implant/device surface).

[0168] A preferred polymeric matrix which can be used to help prevent the formation of fibrous or gliotic tissue around the CRM lead and electrode, either alone or in combination with a fibrosis (or gliosis) inhibiting agent/composition, is formed from reactants comprising either one or both of pentaerythritol poly(ethylene glycol)ether tetra-sulfhydryl] (4-armed thiol PEG, which includes structures having a linking group(s) between a sulfhydryl group(s) and the terminus of the polyethylene glycol backbone) and pentaerythritol poly(ethylene glycol)ether tetra-succinimidyl glutarate] (4-armed NHS PEG, which again includes structures having a linking group(s) between a NHS group(s) and the terminus of the polyethylene glycol backbone) as reactive reagents. Another preferred composition comprises either one or both of pentaerythritol poly(ethylene glycol)ether tetra-amino] (4-armed amino PEG, which includes structures having a linking group(s) between an amino group(s) and the terminus of the polyethylene glycol backbone) and pentaerythritol poly(ethylene glycol)ether tetra-succinimidyl glutarate] (4-armed NHS PEG, which again includes structures having a linking group(s) between a NHS group(s) and the terminus of the polyethylene glycol backbone) as reactive reagents. Chemical structures for these reactants are shown in, e.g., U.S. Pat. No. 5,874,500. Optionally, collagen or a collagen derivative (e.g., methylated collagen) is added to the poly(ethylene glycol)-containing reactant(s) to form a preferred crosslinked matrix that can serve as a polymeric carrier for a therapeutic agent or a stand-alone composition to help prevent the formation of fibrous or gliotic tissue around the CRM lead and electrode.

[0169] It should be apparent to one of skill in the art that potentially any anti-scarring agent described herein may be utilized alone, or in combination, in the practice of this embodiment. As CRM devices, leads and electrodes are made in a variety of configurations and sizes, the exact dose administered may vary with device size, surface area and

design. However, certain principles can be applied in the application of this art. Drug dose can be calculated as a function of dose per unit area (of the portion of the device being coated), total drug dose administered can be measured, and appropriate surface concentrations of active drug can be determined. Regardless of the method of application of the drug to the device (i.e., as a coating or infiltrated into the surrounding tissue), the fibrosis-inhibiting agents, used alone or in combination, may be administered under the following dosing guidelines:

[0170] Drugs and dosage: Exemplary therapeutic agents that may be used include, but are not limited to: antimicrotubule agents including taxanes (e.g., paclitaxel and docetaxel), other microtubule stabilizing agents, mycophenolic acid, rapamycin and vinca alkaloids (e.g., vinblastine and vincristine sulfate). Drugs are to be used at concentrations that range from several times more than a single systemic dose (e.g., the dose used in oral or i.v. administration) to a fraction of a single systemic dose (e.g., 10%, 5%, or even less than 1% of the concentration typically used in a single systemic dose application). Preferably, the drug is released in effective concentrations for a period ranging from 1-90 days. Antimicrotubule agents including taxanes, such as paclitaxel and analogues and derivatives (e.g., docetaxel) thereof, and vinca alkaloids, including vinblastine and vincristine sulfate and analogues and derivatives thereof, should be used under the following parameters: total dose not to exceed 10 mg (range of 0.1 μg to 10 mg); preferred total dose 1 μg to 3 mg. Dose per unit area of the device of 0.1 μg-10 μg per mm^2; preferred dose/unit area of 0.25 $\mu g/mm^2$-5 $\mu g/mm^2$. Minimum concentration of 10^{-8}-10^{-4} M of drug is to be maintained on the device surface. Immunomodulators including sirolimus and everolimus. Sirolimus (i.e., rapamycin, RAPAMUNE): Total dose not to exceed 10 mg (range of 0.1 μg to 10 mg); preferred 10 μg to 1 mg. The dose per unit area of 0.1 μg-100 μg per mm^2; preferred dose of 0.5 $\mu g/mm^2$-10 $\mu g/mm^2$. Minimum concentration of 10^{-8}-10^{-4} M is to be maintained on the device surface. Everolimus and derivatives and analogues thereof: Total dose should not exceed 10 mg (range of 0.1 μg to 10 mg); preferred 10 μg to 1 mg. The dose per unit area of 0.1 μg-100 μg per mm^2 of surface area; preferred dose of 0.3 $\mu g/mm^2$-10 $\mu g/mm^2$. Minimum concentration of 10^{-8}-10^{-4} M of everolimus is to be maintained on the device surface. Inosine monophosphate dehydrogenase inhibitors (e.g., mycophenolic acid, 1-alpha-25 dihydroxy vitamin D_3) and analogues and derivatives thereof: total dose not to exceed 2000 mg (range of 10.0 μg to 2000 mg); preferred 10 μg to 300 mg. The dose per unit area of the device of 1.0 μg-1000 μg per mm^2; preferred dose of 2.5 $\mu g/mm^2$-500 $\mu g/mm^2$. Minimum concentration of 10^{-8}-10^{-3} M of mycophenolic acid is to be maintained on the device surface.

[0171] B. Therapeutic Agents for Use with Electrical Medical Devices and Implants

[0172] As described previously, numerous therapeutic agents are potentially suitable to inhibit fibrous (or glial) tissue accumulation around the device bodies, leads and electrodes of implantable electrical devices, e.g., neurostimulation and cardiac rhythm management devices. The invention provides for devices that include an agent that inhibits this tissue accumulation in the vicinity of the device, i.e., between the medical device and the host into which the medical device is implanted. The agent is therefore effective for this goal, is present in an amount that is effective to achieve this goal, and is present at one or more locations that allow for this goal to be achieved, and the device is designed to allow the beneficial effects of the agent to occur. Also, these therapeutic agents can be used alone, or in combination, to prevent scar (or glial) tissue build-up in the vicinity of the electrode-tissue interface in order to improve the clinical performance and longevity of these implants.

[0173] Suitable fibrosis or gliosis-inhibiting agents may be readily identified based upon in vitro and in vivo (animal) models, such as those provided in Examples 38-51. Agents which inhibit fibrosis can also be identified through in vivo models including inhibition of intimal hyperplasia development in the rat balloon carotid artery model (Examples 43 and 51). The assays set forth in Examples 42 and 50 may be used to determine whether an agent is able to inhibit cell proliferation in fibroblasts and/or smooth muscle cells. In one aspect of the invention, the agent has an IC_{50} for inhibition of cell proliferation within a range of about 10^{-6} to about 10^{-10} M. The assay set forth in Example 46 may be used to determine whether an agent may inhibit migration of fibroblasts and/or smooth muscle cells. In one aspect of the invention, the agent has an IC_{50} for inhibition of cell migration within a range of about 10^{-6} to about 10^{-9}M. Assays set forth herein may be used to determine whether an agent is able to inhibit inflammatory processes, including nitric oxide production in macrophages (Example 38), and/or TNF-alpha production by macrophages (Example 39), and/or IL-1 beta production by macrophages (Example 47), and/or IL-8 production by macrophages (Example 48), and/or inhibition of MCP-1 by macrophages (Example 49). In one aspect of the invention, the agent has an IC_{50} for inhibition of any one of these inflammatory processes within a range of about 10^{-6} to about 10^{-10}M. The assay set forth in Example 44 may be used to determine whether an agent is able to inhibit MMP production. In one aspect of the invention, the agent has an IC_{50} for inhibition of MMP production within a range of about 10^{-4} to about 10^{-8}M. The assay set forth in Example 45 (also known as the CAM assay) may be used to determine whether an agent is able to inhibit angiogenesis. In one aspect of the invention, the agent has an IC_{50} for inhibition of angiogenesis within a range of about 10^{-6} to about 10^{-10}M. Agents which reduce the formation of surgical adhesions may be identified through in vivo models including the rabbit surgical adhesions model (Example 41) and the rat caecal sidewall model (Example 40). These pharmacologically active agents (described below) can then be delivered at appropriate dosages (described herein) into to the tissue either alone, or via carriers (formulations are described herein), to treat the clinical problems described previously herein. Numerous therapeutic compounds have been identified that are of utility in the present invention including:

[0174] 1) Angiogenesis Inhibitors

[0175] In one embodiment, the pharmacologically active compound is an angiogenesis inhibitor (e.g., 2-ME (NSC-659853), PI-88 (D-mannose, O-6-O-phosphono-alpha-D-mannopyranosyl-(1-3)-O-alpha-D-mannopyranosyl-(1-3)-O-alpha-D-mannopyranosyl-(1-3)-O-alpha-D-mannopyranosyl-(1-2)-hydrogen sulphate), thalidomide (1H-isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)-), CDC-394, CC-5079, ENMD-0995 (S-3-amino-phthalidoglutarimide), AVE-8062A, vatalanib, SH-268, halofuginone hydrobromide, atiprimod dimaleate (2-azaspivo[4.5]decane-2-propanamine, N,N-diethyl-8,8-dipropyl, dimaleate), ATN-224, CHIR-258, combretastatin A-4 (phenol, 2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]-, (Z)-), GCS-100LE, or an analogue or derivative thereof).

[0176] 2) 5-Lipoxygenase Inhibitors and Antagonists

[0177] In another embodiment, the pharmacologically active compound is a 5-lipoxygenase inhibitor or antagonist (e.g., Wy-50295 (2-naphthaleneacetic acid, alpha-methyl-6-(2-quinolinylmethoxy)-, (S)-), ONO-LP-269 (2,11,14-eicosatrienamide, N-(4-hydroxy-2-(1H-tetrazol-5-yl)-8-quinolinyl)-, (E,Z,Z)-), licofelone (1H-pyrrolizine-5-acetic acid, 6-(4-chlorophenyl)-2,3-dihydro-2,2-dimethyl-7-phenyl-), CMI-568 (urea, N-butyl-N-hydroxy-N'-(4-(3-(methylsulfonyl)-2-propoxy-5-(tetrahydro-5-(3,4,5-trimethoxyphenyl)-2-furanyl)phenoxy)butyl)-,trans-), IP-751 ((3R,4R)-(delta 6)-THC-DMH-11-oic acid), PF-5901 (benzenemethanol, alpha-pentyl-3-(2-quinolinylmethoxy)-), LY-293111 (benzoic acid, 2-(3-(3-((5-ethyl-4'-fluoro-2-hydroxy(1,1'-biphenyl)-4-yl)oxy)propoxy)-2-propylphenoxy)-), RG-5901-A (benzenemethanol, alpha-pentyl-3-(2-quinolinylmethoxy)-, hydrochloride), rilopirox (2(1H)-pyridinone, 6-((4-(4-chlorophenoxy)phenoxy)methyl)-1-hydroxy-4-methyl-), L-674636 (acetic acid, ((4-(4-chlorophenyl)-1-(4-(2-quinolinylmethoxy)phenyl)butyl)thio)-AS)), 7-((3-(4-methoxytetrahydro-2H-pyran-4-yl)phenyl)methoxy)-4-phenylnaphtho(2,3-c)furan-1 (3H)-one, MK-886 (1H-indole-2-propanoic acid, 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-alpha, alpha-dimethyl-5-(1-methylethyl)-), quiflapon (1H-indole-2-propanoic acid,1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-alpha, alpha-dimethyl-5-(2-quinolinylmethoxy)-), quiflapon (1H-Indole-2-propanoic acid, 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-alpha, alpha-dimethyl-5-(2-quinolinylmethoxy)-), docebenone (2,5-cyclohexadiene-1,4-dione, 2-(12-hydroxy-5,10-dodecadiynyl)-3,5,6-trimethyl-), zileuton (urea, N-(1-benzo(b)thien-2-ylethyl)-N-hydroxy-), or an analogue or derivative thereof).

[0178] 3) Chemokine Receptor Antagonists CCR (1, 3, and 5)

[0179] In another embodiment, the pharmacologically active compound is a chemokine receptor antagonist which inhibits one or more subtypes of CCR (1, 3, and 5) (e.g., ONO-4128 (1,4,9-triazaspiro(5.5)undecane-2,5-dione, 1-butyl-3-(cyclohexylmethyl)-9-((2,3-dihydro-1,4-benzodioxin-6-yl)methyl-), L-381, CT-112 (L-arginine, L-threonyl-L-threonyl-L-seryl-L-glutaminyl-L-valyl-L-arginyl-L-prolyl-), AS-900004, SCH-C, ZK-811752, PD-172084, UK-427857, SB-380732, vMIP II, SB-265610, DPC-168, TAK-779 (N,N-dimethyl-N-(4-(2-(4-methylphenyl)-6,7-dihydro-5H-benzocyclohepten-8-ylcarboxamido)benyl)tetrahydro-2H-pyran-4-aminium chloride), TAK-220, KRH-1120), GSK766994, SSR-150106, or an analogue or derivative thereof). Other examples of chemokine receptor antagonists include a-Immunokine-NNS03, BX-471, CCX-282, Sch-350634; Sch-351125; Sch-417690; SCH-C, and analogues and derivatives thereof.

[0180] 4) Cell Cycle Inhibitors

[0181] In another embodiment, the pharmacologically active compound is a cell cycle inhibitor. Representative examples of such agents include taxanes (e.g., paclitaxel (discussed in more detail below) and docetaxel) (Schiff et al., *Nature* 277:665-667, 1979; Long and Fairchild, *Cancer Research* 54:4355-4361, 1994; Ringel and Horwitz, *J. Natl Cancer Inst.* 83(4):288-291, 1991; Pazdur et al., *Cancer Treat. Rev.* 19(40):351-386, 1993), etanidazole, nimorazole (B. A. Chabner and D. L. Longo. Cancer Chemotherapy and Biotherapy—Principles and Practice. Lippincott-Raven Publishers, New York, 1996, p. 554), perfluorochemicals with hyperbaric oxygen, transfusion, erythropoietin, BW12C, nicotinamide, hydralazine, BSO, WR-2721, IudR, DUdR, etanidazole, WR-2721, BSO, mono-substituted keto-aldehyde compounds (L. G. Egyud. Keto-aldehyde-amine addition products and method of making same. U.S. Pat. No. 4,066,650, Jan. 3, 1978), nitroimidazole (K. C. Agrawal and M. Sakaguchi. Nitroimidazole radiosensitizers for Hypoxic tumor cells and compositions thereof. U.S. Pat. No. 4,462,992, Jul. 31, 1984), 5-substituted-4-nitroimidazoles (Adams et al., *Int. J. Radiat. Biol. Relat. Stud. Phys., Chem. Med.* 40(2):153-61, 1981), SR-2508 (Brown et al., *Int. J. Radiat. Oncol., Biol. Phys.* 7(6):695-703, 1981), 2H-isoindolediones (J. A. Myers, 2H-Isoindolediones, the synthesis and use as radiosensitizers. U.S. Pat. No. 4,494,547, Jan. 22, 1985), chiral (((2-bromoethyl)-amino)methyl)-nitro-1H-imidazole-1-ethanol (V. G. Beylin, et al., Process for preparing chiral (((2-bromoethyl)-amino)methyl)-nitro-1H-imidazole-1-ethanol and related compounds. U.S. Pat. No. 5,543,527, Aug. 6, 1996; U.S. Pat. No. 4,797,397; Jan. 10, 1989; U.S. Pat. No. 5,342,959, Aug. 30, 1994), nitroaniline derivatives (W. A. Denny, et al. Nitroaniline derivatives and the use as anti-tumor agents. U.S. Pat. No. 5,571,845, Nov. 5, 1996), DNA-affinic hypoxia selective cytotoxins (M. V. Papadopoulou-Rosenzweig. DNA-affinic hypoxia selective cytotoxins. U.S. Pat. No. 5,602,142, Feb. 11, 1997), halogenated DNA ligand (R. F. Martin. Halogenated DNA ligand radiosensitizers forcancer therapy. U.S. Pat. No. 5,641,764, Jun. 24, 1997), 1,2,4 benzotriazine oxides (W. W. Lee et al. 1,2,4-benzotriazine oxides as radiosensitizers and selective cytotoxic agents. U.S. Pat. No. 5,616,584, Apr. 1, 1997; U.S. Pat. No. 5,624,925, Apr. 29, 1997; Process for Preparing 1,2,4 Benzotriazine oxides. U.S. Pat. No. 5,175,287, Dec. 29, 1992), nitric oxide (J. B. Mitchell et al., Use of Nitric oxide releasing compounds as hypoxic cell radiation sensitizers. U.S. Pat. No. 5,650,442, Jul. 22, 1997), 2-nitroimidazole derivatives (M. J. Suto et al. 2-Nitroimidazole derivatives useful as radiosensitizers for hypoxic tumor cells. U.S. Pat. No. 4,797,397, Jan. 10, 1989; T. Suzuki. 2-Nitroimidazole derivative, production thereof, and radiosensitizer containing the same as active ingredient. U.S. Pat. No. 5,270,330, Dec. 14, 1993; T. Suzuki et al. 2-Nitroimidazole derivative, production thereof, and radiosensitizer containing the same as active ingredient. U.S. Pat. No. 5,270,330, Dec. 14, 1993; T. Suzuki. 2-Nitroimidazole derivative, production thereof and radiosensitizer containing the same as active ingredient; Patent EP 0 513 351 B1, Jan. 24, 1991), fluorine-containing nitroazole derivatives (T. Kagiya. Fluorine-containing nitroazole derivatives and radiosensitizer comprising the same. U.S. Pat. No. 4,927,941, May 22, 1990), copper (M. J. Abrams. Copper Radiosensitizers. U.S. Pat. No. 5,100,885, Mar. 31, 1992), combination modality cancer therapy (D. H. Picker et al. Combination modality cancer therapy. U.S. Pat. No. 4,681,091, Jul. 21, 1987). 5-CldC or (d)H_4U or 5-halo-2'-halo-2'-deoxy-cytidine or -uridine derivatives (S. B. Greer. Method and Materials for sensitizing neoplastic tissue to radiation. U.S. Pat. No. 4,894,364 Jan. 16, 1990), platinum complexes (K. A. Skov. Platinum Complexes with one radiosensitizing ligand. U.S. Pat. No. 4,921,963. May 1, 1990; K. A. Skov. Platinum Complexes with one radiosensitizing ligand. Patent EP 0 287 317 A3), fluorine-containing nitroazole (T. Kagiya, et al. Fluorine-containing nitroazole derivatives and radiosensitizer comprising the same. U.S. Pat. No. 4,927,941. May 22, 1990), benzamide (W. W. Lee. Substituted Benzamide Radiosensitizers. U.S. Pat. No. 5,032,617, Jul. 16, 1991), autobiotics (L. G. Egyud. Autobiotics and the use in eliminating nonself cells in vivo. U.S. Pat. No. 5,147,652. Sep. 15, 1992), benzamide and nicotinamide (W. W. Lee et al. Benzamide and Nictoinamide

Radiosensitizers. U.S. Pat. No. 5,215,738, Jun. 1, 1993), acridine-intercalator (M. Papadopoulou-Rosenzweig. Acridine Intercalator based hypoxia selective cytotoxins. U.S. Pat. No. 5,294,715, Mar. 15, 1994), fluorine-containing nitroimidazole (T. Kagiya et al. Fluorine containing nitroimidazole compounds. U.S. Pat. No. 5,304,654, Apr. 19, 1994), hydroxylated texaphyrins (J. L. Sessler et al. Hydroxylated texaphrins. U.S. Pat. No. 5,457,183, Oct. 10, 1995), hydroxylated compound derivative (T. Suzuki et al. Heterocyclic compound derivative, production thereof and radiosensitizer and antiviral agent containing said derivative as active ingredient. Publication Number 011106775 A (Japan), Oct. 22, 1987; T. Suzuki et al. Heterocyclic compound derivative, production thereof and radiosensitizer, antiviral agent and anti cancer agent containing said derivative as active ingredient. Publication Number 01139596 A (Japan), Nov. 25, 1987; S. Sakaguchi et al. Heterocyclic compound derivative, its production and radiosensitizer containing said derivative as active ingredient; Publication Number 63170375 A (Japan), Jan. 7, 1987), fluorine containing 3-nitro-1,2,4-triazole (T. Kagitani et al. Novel fluorine-containing 3-nitro-1,2,4-triazole and radiosensitizer containing same compound. Publication Number 02076861 A (Japan), Mar. 31, 1988), 5-thiotretrazole derivative or its salt (E. Kano et al. Radiosensitizer for Hypoxic cell. Publication Number 61010511 A (Japan), Jun. 26, 1984), Nitrothiazole (T. Kagitani et al. Radiation-sensitizing agent. Publication Number 61167616 A (Japan) Jan. 22, 1985), imidazole derivatives (S. Inayma et al. Imidazole derivative. Publication Number 6203767 A (Japan) Aug. 1, 1985; Publication Number 62030768 A (Japan) Aug. 1, 1985; Publication Number 62030777 A (Japan) Aug. 1, 1985), 4-nitro-1,2,3-triazole (T. Kagitani et al. Radiosensitizer. Publication Number 62039525 A (Japan), Aug. 15, 1985), 3-nitro-1,2,4-triazole (T. Kagitani et al. Radiosensitizer. Publication Number 62138427 A (Japan), Dec. 12, 1985), Carcinostatic action regulator (H. Amagase. Carcinostatic action regulator. Publication Number 63099017 A (Japan), Nov. 21, 1986), 4,5-dinitroimidazole derivative (S. Inayama. 4,5-Dinitroimidazole derivative. Publication Number 63310873 A (Japan) Jun. 9, 1987), nitrotriazole Compound (T. Kagitanil Nitrotriazole Compound. Publication Number 07149737 A (Japan) Jun. 22, 1993), cisplatin, doxorubin, misonidazole, mitomycin, tiripazamine, nitrosourea, mercaptopurine, methotrexate, fluorouracil, bleomycin, vincristine, carboplatin, epirubicin, doxorubicin, cyclophosphamide, vindesine, etoposide (I. F. Tannock. Review Article: Treatment of Cancer with Radiation and Drugs. *Journal of Clinical Oncology* 14(12):3156-3174, 1996), camptothecin (Ewend M. G. et al. Local delivery of chemotherapy and concurrent external beam radiotherapy prolongs survival in metastatic brain tumor models. *Cancer Research* 56(22):5217-5223, 1996) and paclitaxel (Tishler R. B. et al. Taxol: a novel radiation sensitizer. *International Journal of Radiation Oncology and Biological Physics* 22(3):613-617, 1992).

[**0182**] A number of the above-mentioned cell cycle inhibitors also have a wide variety of analogues and derivatives, including, but not limited to, cisplatin, cyclophosphamide, misonidazole, tiripazamine, nitrosourea, mercaptopurine, methotrexate, fluorouracil, epirubicin, doxorubicin, vindesine and etoposide. Analogues and derivatives include $(CPA)_2Pt(DOLYM)$ and (DACH)Pt(DOLYM) cisplatin (Choi et al., *Arch. Pharmacal Res.* 22(2):151-156, 1999), Cis-($PtCl_2$(4,7-H-5-methyl-7-oxo)1,2,4(triazolo(1,5-a)pyrimidine)$_2$) (Navarro et al., *J. Med. Chem.* 41(3):332-338, 1998), (Pt(cis-1,4-DACH)(trans-Cl_2)(CBDCA)).½MeOH cisplatin (Shamsuddin et al., *Inorg. Chem.* 36(25):5969-5971, 1997), 4-pyridoxate diammine hydroxy platinum (Tokunaga et al., *Pharm. Sci.* 3(7):353-356, 1997), Pt(II) . . . Pt(II) ($Pt_2(NHCHN(C(CH_2)(CH_3)))_4$) (Navarro et al., *Inorg. Chem.* 35(26):7829-7835, 1996), 254-S cisplatin analogue (Koga et al., *Neurol. Res.* 18(3):244-247, 1996), o-phenylenediamine ligand bearing cisplatin analogues (Koeckerbauer & Bednarski, *J. Inorg. Biochem.* 62(4):281-298, 1996), trans,cis-($Pt(OAc)_{212}$(en)) (Kratochwil et al., *J. Med. Chem.* 39(13):2499-2507, 1996), estrogenic 1,2-diarylethylenediamine ligand (with sulfur-containing amino acids and glutathione) bearing cisplatin analogues (Bednarski, *J. Inorg. Biochem.* 62(1):75, 1996), cis-1,4-diaminocyclohexane cisplatin analogues (Shamsuddin et al., *J. Inorg. Biochem.* 61(4):291-301, 1996), 5' orientational isomer of cis-($Pt(NH_3)$(4-aminoTEMP-O){d(GpG)}) (Dunham & Lippard, *J. Am. Chem. Soc.* 117(43):10702-12, 1995), chelating diamine-bearing cisplatin analogues (Koeckerbauer & Bednarski, *J. Pharm. Sci.* 84(7):819-23, 1995), 1,2-diarylethyleneamine ligand-bearing cisplatin analogues (Otto et al., *J. Cancer Res. Clin. Oncol.* 121(1):31-8, 1995), (ethylenediamine)platinum(II) complexes (Pasini et al., *J. Chem. Soc., Dalton Trans.* 4:579-85, 1995), CI-973 cisplatin analogue (Yang et al., *Int. J. Oncol.* 5(3):597-602, 1994), cis-diamminedichloroplatinum(II) and its analogues cis-1,1-cyclobutanedicarbosylato(2R)-2-methyl-1,4-butanediammineplatinum(II) and cis-diammine(glycolato)platinum (Claycamp & Zimbrick, *J. Inorg. Biochem.,* 26(4):257-67, 1986; Fan et al., *Cancer Res.* 48(11):3135-9, 1988; Heiger-Bemays et al., *Biochemistry* 29(36):8461-6, 1990; Kikkawa et al., *J. Exp. Clin. Cancer Res.* 12(4):233-40, 1993; Murray et al., *Biochemistry* 31(47):11812-17, 1992; Takahashi et al., *Cancer Chemother. Pharmacol.* 33(1):31-5, 1993), cis-amine-cyclohexylamine-dichloroplatinum(II) (Yoshida et al., *Biochem. Pharmacol.* 48(4):793-9, 1994), gem-diphosphonate cisplatin analogues (FR 2683529), (meso-1,2-bis(2,6-dichloro-4-hydroxyplenyl)ethylenediamine) dichloroplatinum(II) (Bednarski et al., *J. Med. Chem.* 35(23):4479-85, 1992), cisplatin analogues containing a tethered dansyl group (Hartwig et al., *J. Am. Chem. Soc.* 114(21):8292-3, 1992), platinum(II) polyamines (Siegmann et al., *Inorg. Met.-Containing Polym. Mater.*, (*Proc. Am. Chem. Soc. Int. Symp.*), 335-61, 1990), cis-(3H)dichloro(ethylenediamine-)platinum(II) (Eastman, *Anal. Biochem.* 197(2):311-15, 1991), trans-diamminedichloroplatinum(II) and cis-($Pt(NH_3)_2(N_3$-cytosine)Cl) (Bellon & Lippard, *Biophys. Chem.* 35(2-3):179-88, 1990), 3H-cis-1,2-diaminocyclohexanedichloroplatinum(II) and 3H-cis-1,2-diaminocyclohexane-malonatoplatinum (II) (Oswald et al., *Res. Commun. Chem. Pathol. Pharmacol.* 64(1):41-58, 1989), diaminocarboxylatoplatinum (EPA 296321), trans-(D,1)-1,2-diaminocyclohexane carrier ligand-bearing platinum analogues (Wyrick & Chaney, *J. Labelled Compd. Radiopharm.* 25(4):349-57, 1988), aminoalkylaminoanthraquinone-derived cisplatin analogues (Kitov et al., *Eur. J. Med. Chem.* 23(4):381-3, 1988), spiroplatin, carboplatin, iproplatin and JM40 platinum analogues (Schroyen et al., *Eur. J. Cancer Clin. Oncol.* 24(8):1309-12, 1988), bidentate tertiary diamine-containing cisplatinum derivatives (Orbell et al., *Inorg. Chim. Acta* 152(2):125-34, 1988), platinum(II), platinum(IV) (Liu & Wang, *Shandong Yike Daxue Xuebao* 24(1):35-41, 1986), cis-diammine(1,1-cyclobutanedicarboxylato-)platinum(II) (carboplatin, JM8) and ethylenediammine-malonatoplatinum(II) (JM40) (Begg et al., *Radiother. Oncol.* 9(2):157-65, 1987), JM8 and JM9 cisplatin analogues (Harstrick et al., *Int. J. Androl.* 10(1); 139-45, 1987), (NPr4)2((PtCL4).cis-(PtCl2-($NH2Me)_2$)) (Brammer

et al., *J. Chem. Soc., Chem. Commun.* 6:443-5, 1987), aliphatic tricarboxylic acid platinum complexes (EPA 185225), cis-dichloro(amino acid)(tert-butylamine)platinum(II) complexes (Pasini & Bersanetti, *Inorg. Chim. Acta* 107(4):259-67, 1985); 4-hydroperoxycylcophosphamide (Ballard et al., *Cancer Chemother. Pharmacol.* 26(6):397-402, 1990), acyclouridine cyclophosphamide derivatives (Zakerinia et al., *Helv. Chim. Acta* 73(4):912-15, 1990), 1,3,2-dioxa- and -oxazaphosphorinane cyclophosphamide analogues (Yang et al., *Tetrahedron* 44(20):6305-14, 1988), C5-substituted cyclophosphamide analogues (Spada, University of Rhode Island Dissertation, 1987), tetrahydrooxazine cyclophosphamide analogues (Valente, University of Rochester Dissertation, 1988), phenyl ketone cyclophosphamide analogues (Hales et al., *Teratology* 39(1):31-7, 1989), phenylketophosphamide cyclophosphamide analogues (Ludeman et al., *J. Med. 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Nat'l Cancer Inst.* 89(16):1217-1223, 1997), 4-demethoxy-7-O-(2,6-dideoxy-4-O-(2,3,6-trideoxy-3-amino-α-L-lyxo-hexopyranosyl)-α-L-lyxo-hexopyranosyl)-adriamicinone doxorubicin disaccharide analogue (Monteagudo et al., *Carbohydr. Res.* 300(1):11-16, 1997), 2-pyrrolinodoxorubicin (Nagy et al., *Proc. Nat'l Acad. Sci. U.S.A.* 94(2):652-656, 1997), morpholinyl doxorubicin analogues (Duran et al., *Cancer Chemother. Pharmacol.* 38(3):210-216, 1996), enaminomalonyl-α-alanine doxorubicin derivatives (Seitz et al., *Tetrahedron Lett.* 36(9):1413-16, 1995), cephalosporin doxorubicin derivatives (Vrudhula et al., *J. Med. Chem.* 38(8):1380-5, 1995), hydroxyrubicin (Solary et al., *Int. J. Cancer* 58(1):85-94, 1994), methoxymorpholino doxorubicin derivative (Kuhl et al., *Cancer Chemother. Pharmacol.* 33(1):10-16, 1993), (6-maleimidocaproyl)hydrazone doxorubicin derivative (Wiliner et al., *Bioconjugate Chem.* 4(6):521-7, 1993), N-(5, 5-diacetoxypent-1-yl) doxorubicin (Cherif & Farquhar, *J. Med. Chem.* 35(17):3208-14, 1992), FCE 23762 methoxymorpholinyl doxorubicin derivative (Ripamonti et al., *Br. J. Cancer* 65(5):703-7, 1992), N-hydroxysuccinimide ester doxorubicin derivatives (Demant et al., *Biochim. Biophys. Acta* 1118(1):83-90, 1991), polydeoxynucleotide doxorubicin derivatives (Ruggiero et al., *Biochim. Biophys. Acta* 1129(3):294-302, 1991), morpholinyl doxorubicin derivatives (EPA 434960), mitoxantrone doxorubicin analogue (Krapcho et al., *J. Med. Chem.* 34(8):2373-80. 1991), AD198 doxorubicin analogue (Traganos et al., *Cancer Res.* 51(14):3682-9, 1991), 4-demethoxy-3'-N-trifluoroacetyidoxorubicin (Horton et al., *Drug Des. Delivery* 6(2):123-9, 1990), 4'-epidoxorubicin (Drzewoski et al., *Pol. J. Pharmacol. Pharm.* 40(2):159-65, 1988; Weenen et al., *Eur. J. Cancer Clin. Oncol.* 20(7):919-26, 1984), alkylating cyanomorpholino doxorubicin derivative (Scudder et al., *J. Nat'l Cancer Inst.* 80(16):1294-8, 1988), deoxydihydroiodooxorubicin (EPA 275966), adriblastin (Kalishevskaya et al., *Vestn. Mosk. Univ.,* 16(Biol. 1):21-7, 1988), 4'-deoxydoxorubicin (Schoeizel et al., *Leuk. Res.* 10(12):1455-9, 1986), 4-demethyoxy-4'-o-methyldoxorubicin (Giuliani et al., *Proc. Int. Congr. Chemother.* 16:285-70-285-77, 1983), 3'-deamino-3'-hydroxydoxorubicin (Horton et al., *J. Antibiot.* 37(8):853-8, 1984), 4-demethyoxy doxorubicin analogues (Barbieri et al., *Drugs Exp. Clin. Res.* 10(2):85-90, 1984), N-L-leucyl doxorubicin derivatives (Trouet et al., *Anthracyclines (Proc. Int. Symp. Tumor Pharmacother.)*, 179-81, 1983), 3'-deamino-3'-(4-methoxy-1-piperidinyl) doxorubicin derivatives (U.S. Pat. No. 4,314,054), 3'-deamino-3'-(4-mortholinyl) doxorubicin derivatives (U.S. Pat. No. 4,301,277), 4'-deoxydoxorubicin and 4'-o-methyldoxorubicin (Giuliani et al., *Int. J. Cancer* 27(1):5-13, 1981), aglycone doxorubicin derivatives (Chan & Watson, *J. Pharm. Sci.* 67(12):1748-52, 1978), SM 5887 (*Pharma Japan* 1468:20, 1995), MX-2 (Pharma Japan 1420:19, 1994), 4'-deoxy-13(S)-dihydro-4'-iododoxorubicin (EP 275966), morpholinyl doxorubicin derivatives (EPA 434960), 3'-deamino-3'-(4-methoxy-1-piperidinyl) doxorubicin derivatives (U.S. Pat. No. 4,314,054), doxorubicin-14-valerate, morpholinodoxorubicin (U.S. Pat. No. 5,004,606), 3'-deamino-3'-(3"-cyano-4"-morpholinyl doxorubicin; 3'-deamino-3'-(3"-cyano-4"-morpholinyl)-13-dihydoxorubicin; (3'-deamino-3'-(3"-cyano-4"-morpholinyl) daunorubicin; 3'-deamino-3'-(3"-cyano-4"-morpholinyl)-3-dihydrodaunorubicin; and 3'-deamino-3'-(4"-morpholinyl-5-iminodoxorubicin and derivatives (U.S. Pat. No. 4,585,859), 3'-deamino-3'-(4-methoxy-1-piperidinyl) doxorubicin derivatives (U.S. Pat. No. 4,314,054) and 3-deamino-3-(4-morpholinyl) doxorubicin derivatives (U.S. Pat. No. 4,301, 277); 4,5-dimethylmisonidazole (Bom et al., *Biochem. Pharmacol.* 43(6):1337-44, 1992), azo and azoxy misonidazole derivatives (Gattavecchia & Tonelli, *Int. J. Radiat. Biol. Relat. Stud. Phys., Chem. Med.* 45(5):469-77, 1984); RB90740 (Wardman et al., *Br. J. Cancer,* 74 *Suppl.* (27):S70-S74, 1996); 6-bromo and 6-chloro-2,3-dihydro-1, 4-benzothiazines nitrosourea derivatives (Rai et al., *Heterocycl. Commun.* 2(6):587-592, 1996), diamino acid nitrosourea derivatives (Dulude et al., *Bioorg. Med. Chem. Lett.* 4(22):2697-700, 1994; Dulude et al., *Bioorg. Med. Chem.* 3(2):151-60, 1995), amino acid nitrosourea derivatives (Zheleva et al., *Pharmazie* 50(1):25-6, 1995), 3',4'-didemethoxy-3',4'-dioxo-4-deoxypodophyllotoxin nitrosourea derivatives (Miyahara et al., *Heterocycles* 39(1):361-9, 1994), ACNU (Matsunaga et al., *Immunopharmacology* 23(3):199-204, 1992), tertiary phosphine oxide

nitrosourea derivatives (Guguva et al., *Pharmazie* 46(8):603, 1991), sulfamerizine and sulfamethizole nitrosourea derivatives (Chiang et al., *Zhonghua Yaozue Zazhi* 43(5):401-6, 1991), thymidine nitrosourea analogues (Zhang et al., *Cancer Commun.* 3(4): 119-26, 1991),1,3-bis(2-chloroethyl)-1-nitrosourea (August et al., *Cancer Res.* 51(6):1586-90, 1991), 2,2,6,6-tetramethyl-1-oxopiperidiunium nitrosourea derivatives (U.S.S.R. 1261253), 2- and 4-deoxy sugar nitrosourea derivatives (U.S. Pat. No. 4,902, 791), nitroxyl nitrosourea derivatives (U.S.S.R. 1336489), fotemustine (Boutin et al., *Eur. J. Cancer Clin. Oncol.* 25(9):1311-16, 1989), pyrimidine (II) nitrosourea derivatives (Wei et al., *Chung-hua Yao Hsuch Tsa Chih* 41(1):19-26, 1989), CGP 6809 (Schieweck et al., *Cancer Chemother. Pharmacol.* 23(6):341-7, 1989), B-3839 (Prajda et al., In Vivo 2(2):151-4, 1988), 5-halogenocytosine nitrosourea derivatives (Chiang & Tseng, *T'ai-wan Yao Hsuch Tsa Chih* 38(1):37-43, 1986), 1-(2-chloroethyl)-3-isobutyl-3-(β-maltosyl)-1-nitrosourea (Fujimoto & Ogawa, *J. Pharmacobio-Dyn.* 10(7):341-5, 1987), sulfur-containing nitrosoureas (Tang et al., *Yaoxue Xuebao* 21(7):502-9, 1986), sucrose, 6-((((2-chloroethyl)nitrosoamino-)carbonyl)amino)-6-deoxysucrose (NS-1C) and 6'-((((2-chloroethyl)nitrosoamino)carbonyl)amino)-6'-deoxysucrose (NS-1D) nitrosourea derivatives (Tanoh et al., *Chemotherapy* (*Tokyo*) 33(11):969-77, 1985), CNCC, RFCNU and chlorozotocin (Mena et al., *Chemotherapy* (*Basel*) 32(2):131-7, 1986), CNUA (Edanami et al., *Chemotherapy* (*Tokyo*) 33(5):455-61, 1985), 1-(2-chloroethyl)-3-isobutyl-3-(β-maltosyl)-1-nitrosourea (Fujimoto & Ogawa, *Jpn. J. Cancer Res.* (*Gann*) 76(7):651-6, 1985), choline-like nitrosoalkylureas (Belyaev et al., *Izv. Akad. NAUK SSSR, Ser. Khim.* 3:553-7, 1985), sucrose nitrosourea derivatives (JP 84219300), sulfa drug nitrosourea analogues (Chiang et al., *Proc. Nat7 Sci. Counc., Repub. China, Part A* 8(1):18-22, 1984), DONU (Asanuma et al., *J. Jpn. Soc. Cancer Ther.* 17(8):2035-43, 1982), N,N'-bis(N-(2-chloroethyl)-N-nitrosocarbamoyl)cystamine (CNCC) (Blazsek et al., *Toxicol. Appl. Pharmacol.* 74(2):250-7, 1984), dimethylnitrosourea (Krutova et al., *Izv. Akad. NAUK SSSR, Ser. Biol.* 3:439-45, 1984), GANU (Sava & Giraldi, *Cancer Chemother. Pharmacol.* 10(3):167-9, 1983), CCNU (Capelli et al., *Med., Biol., Environ.* 11(1):111-16, 1983), 5-aminomethyl-2'-deoxyuridine nitrosourea analogues (Shiau, *Shih Ta Hsuch Pao* (*Taipei*) 27:681-9, 1982), TA-077 (Fujimoto & Ogawa, *Cancer Chemother. 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Chem.* 22(1):32-5, 1979), glucopyranose nitrosourea derivatives (JP 78 95917), 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (Farmer et al., *J. Med. Chem.* 21(6):514-20, 1978), 4-(3-(2-chloroethyl)-3-nitrosoureid-o)-cis-cyclohexanecarboxylic acid (Drewinko et al., *Cancer Treat. Rep.* 61(8):J1513-18, 1977), RPCNU (ICIG 1163) (Larnicol et al., *Biomedicine* 26(3):J176-81, 1977), IOB-252 (Sorodoc et al., *Rev. Roum. Med., Virol.* 28(1):J 55-61, 1977),1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) (Siebert & Eisenbrand, *Mutat. Res.* 42(1):J45-50, 1977), 1-tetrahydroxycyclopentyl-3-nitroso-3-(2-chloroethyl)-urea (U.S. Pat. No. 4,039, 578), d-1-1-(β-chloroethyl)-3-(2-oxo-3-hexahydroazepinyl)-1-nitrosourea (U.S. Pat. No. 3,859,277) and gentianose nitrosourea derivatives (JP 57080396); 6-S-aminoacyloxymethyl mercaptopurine derivatives (Harada et al., *Chem. Pharm. Bull.* 43(10):793-6, 1995), 6-mercaptopurine (6-MP) (Kashida et al., *Biol. Pharm. Bull.* 18(11):1492-7, 1995), 7,8-polymethyleneimidazo-1,3,2-diazaphosphorines (Nilov et al., *Mendeleev Commun.* 2:67, 1995), azathioprine (Chifotides et al., *J. Inorg. Biochem.* 56(4):249-64, 1994), methyl-D-glucopyranoside mercaptopurine derivatives (Da Silva et al., *Eur. J. Med. Chem.* 29(2):149-52, 1994) and s-alkynyl mercaptopurine derivatives (Ratsino et al., *Khim.-Farm. Zh.* 15(8):65-7, 1981); indoline ring and a modified ornithine or glutamic acid-bearing methotrexate derivatives (Matsuoka et al., *Chem. Pharm. Bull.* 45(7):1146-1150, 1997), alkyl-substituted benzene ring C bearing methotrexate derivatives (Matsuoka et al., *Chem. Pharm. Bull.* 44(12):2287-2293, 1996), benzoxazine or benzothiazine moiety-bearing methotrexate derivatives (Matsuoka et al., *J. Med. Chem.* 40(1):105-111, 1997), 10-deazaminopterin analogues (DeGraw et al., *J. Med. Chem.* 40(3):370-376, 1997), 5-deazaminopterin and 5,10-dideazaminopterin methotrexate analogues (Piper et al., *J. Med. Chem.* 40(3):377-384, 1997), indoline moiety-bearing methotrexate derivatives (Matsuoka et al., *Chem. Pharm. Bull.* 44(7):1332-1337, 1996), lipophilic amide methotrexate derivatives (Pignatello et al., *World Meet. Pharm., Biopharm. Pharm. Technol.,* 563-4, 1995), L-threo-(2S, 4S)-4-fluoroglutamic acid and DL-3,3-difluoroglutamic acid-containing methotrexate analogues (Hart et al., *J. Med. Chem.* 39(1):56-65, 1996), methotrexate tetrahydroquinazoline analogue (Gangjee, et al., *J. Heterocycl. Chem.* 32(1):243-8, 1995), N-(α-aminoacyl) methotrexate derivatives (Cheung et al., *Pteridines* 3(1-2):101-2, 1992), biotin methotrexate derivatives (Fan et al., *Pteridines* 3(1-2):131-2, 1992), D-glutamic acid or D-erythrou, threo-4-fluoroglutamic acid methotrexate analogues (McGuire et al., *Biochem. Pharmacol.* 42(12):2400-3, 1991), β,γ-methano methotrexate analogues (Rosowsky et al., *Pteridines* 2(3):133-9, 1991), 10-deazaminopterin (10-EDAM) analogue (Braakhuis et al., *Chem. Biol. Pteridines, Proc. Int. Symp. Pteridines Folic Acid Deriv.,* 1027-30, 1989), γ-tetrazole methotrexate analogue (Kalman et al., *Chem. Biol. Pteridines, Proc. Int. Symp. Pteridines Folic Acid Deriv.,* 1154-7, 1989), N-(L-α-aminoacyl) methotrexate derivatives (Cheung et al., *Heterocycles* 28(2):751-8, 1989), meta and ortho isomers of aminopterin (Rosowsky et al., *J. Med. Chem.* 32(12):2582, 1989), hydroxymethyl-methotrexate (DE 267495), γ-fluoromethotrexate (McGuire et al., *Cancer Res.* 49(16):4517-25, 1989), polyglutamyl methotrexate derivatives (Kumar et al., *Cancer Res.* 46(10):5020-3, 1986), gem-diphosphonate methotrexate analogues (WO 88/06158), α- and γ-substituted methotrexate analogues (Tsushima et al., *Tetrahedron* 44(17):5375-87, 1988), 5-methyl-5-deaza methotrexate analogues (U.S. Pat. No. 4,725,687), Nδ-acyl-Nα-(4-amino-4-deoxypteroyl)-L-ornithine derivatives (Rosowsky et al., *J. Med. Chem.* 31(7):1332-7, 1988), 8-deaza methotrexate analogues (Kuehl et al., *Cancer Res.* 48(6):1481-8, 1988), acivicin methotrexate analogue (Rosowsky et al., *J. Med. Chem.* 30(8):1463-9, 1987), polymeric platinol methotrexate derivative (Carraher et al., *Polym. Sci. Technol.* (*Plenum*),

35(*Adv. Biomed. Polym.*):311-24, 1987), methotrexate-γ-dimyristoylphophatidylethanolamine (Kinsky et al., *Biochim. Biophys. Acta* 917(2):211-18, 1987), methotrexate polyglutamate analogues (Rosowsky et al., Chem. Biol. Pteridines, Pteridines Folic Acid Deriv., Proc. Int. Symp. Pteridines Folic Acid Deriv.: Chem., Biol. Clin. Aspects: 985-8, 1986), poly-γ-glutamyl methotrexate derivatives (Kisliuk et al., Chem. Biol. Pteridines, Pteridines Folic Acid Deriv., Proc. Int. Symp. Pteridines Folic Acid Deriv.: Chem., Biol. Clin. Aspects: 989-92, 1986), deoxyuridylate methotrexate derivatives (Webber et al., Chem. Biol. Pteridines, Pteridines Folic Acid Deriv., Proc. Int. Symp. Pteridines Folic Acid Deriv.: Chem., Biol. Clin. Aspects: 659-62, 1986), iodoacetyl lysine methotrexate analogue (Delcamp et al., Chem. Biol. Pteridines, Pteridines Folic Acid Deriv., Proc. Int. Symp. Pteridines Folic Acid Deriv.: Chem., Biol. Clin. Aspects: 807-9, 1986), 2,.omega.-diaminoalkanoid acid-containing methotrexate analogues (McGuire et al., *Biochem. Pharmacol.* 35(15):2607-13, 1986), polyglutamate methotrexate derivatives (Kamen & Winick, *Methods Enzymol.* 122 (Vitam. Coenzymes, Pt. G):339-46, 1986), 5-methyl-5-deaza analogues (Piper et al., *J. Med. Chem.* 29(6):1080-7, 1986), quinazoline methotrexate analogue (Mastropaolo et al., *J. Med. Chem.* 29(1):155-8, 1986), pyrazine methotrexate analogue (Lever & Vestal, *J. Heterocycl. Chem.* 22(1):5-6, 1985), cysteic acid and homocysteic acid methotrexate analogues (U.S. Pat. No. 4,490,529), γ-tert-butyl methotrexate esters (Rosowsky et al., *J. Med. Chem.* 28(5):660-7, 1985), fluorinated methotrexate analogues (Tsushima et al., *Heterocycles* 23(1):45-9, 1985), folate methotrexate analogue (Trombe, *J. Bacteriol.* 160(3):849-53, 1984), phosphonoglutamic acid analogues (Sturtz & Guillamot, *Eur. J. Med. Chem.—Chim. Ther.* 19(3):267-73, 1984), poly (L-lysine) methotrexate conjugates (Rosowsky et al., *J. Med. Chem.* 27(7):888-93, 1984), dilysine and trilysine methotrexate derivates (Forsch & Rosowsky, *J. Org. Chem.* 49(7):1305-9, 1984), 7-hydroxymethotrexate (Fabre et al., *Cancer Res.* 43(10):4648-52, 1983), poly-γ-glutamyl methotrexate analogues (Piper & Montgomery, *Adv. Exp. Med. Biol.,* 163(*Folyl Antifolyl Polyglutamates*):95-100, 1983), 3',5'-dichloromethotrexate (Rosowsky & Yu, *J. Med. Chem.* 26(10):1448-52, 1983), diazoketone and chloromethylketone methotrexate analogues (Gangjee et al., *J. Pharm. Sci.* 71(6):717-19, 1982), 10-propargylaminopterin and alkyl methotrexate homologs (Piper et al., *J. Med. Chem.* 25(7):877-80, 1982), lectin derivatives of methotrexate (Lin et al., *JNCI* 66(3):523-8, 1981), polyglutamate methotrexate derivatives (Galivan, *Mol. Pharmacol.* 17(1):105-10, 1980), halogentated methotrexate derivatives (Fox, *JNCI* 58(4):J955-8, 1977), 8-alkyl-7,8-dihydro analogues (Chaykovsky et al., *J. Med. Chem.* 20(10):J1323-7, 1977), 7-methyl methotrexate derivatives and dichloromethotrexate (Rosowsky & Chen, *J. Med. Chem.* 17(12):J1308-11, 1974), lipophilic methotrexate derivatives and 3',5'-dichloromethotrexate (Rosowsky, *J. Med. Chem.* 16(10):J1190-3, 1973), deaza amethopterin analogues (Montgomery et al., *Ann. N.Y. Acad. Sci.* 186:J227-34, 1971), MX068 (Pharma Japan, 1658:18, 1999) and cysteic acid and homocysteic acid methotrexate analogues (EPA 0142220); N3-alkylated analogues of 5-fluorouracil (Kozai et al., *J. Chem. Soc., Perkin Trans.* 1(19):3145-3146, 1998), 5-fluorouracil derivatives with 1,4-oxaheteroepane moieties (Gomez et al., *Tetrahedron* 54(43):13295-13312, 1998), 5-fluorouracil and nucleoside analogues (Li, *Anticancer Res.* 17(1A):21-27, 1997), cis- and trans-5-fluoro-5,6-dihydro-6-alkoxyuracil (Van der Wilt et al., *Br. J. Cancer* 68(4):702-7, 1993), cyclopentane 5-fluorouracil analogues (Hronowski & Szarek, *Can. J. Chem.* 70(4):1162-9, 1992), A-OT-fluorouracil (Zhang et al., *Zongguo Yiyao Gongye Zazhi* 20(11):513-15, 1989), N4-trimethoxybenzoyl-5'-deoxy-5-fluorocytidine and 5'-deoxy-5-fluorouridine (Miwa et al., *Chem. Pharm. Bull.* 38(4):998-1003, 1990), 1-hexylcarbamoyl-5-fluorouracil (Hoshi et al., *J. Pharmacobio-Dun.* 3(9):478-81, 1980; Maehara et al., *Chemotherapy* (Basel) 34(6):484-9, 1988), B-3839 (Prajda et al., *In Vivo* 2(2):151-4, 1988), uracil-1-(2-tetrahydrofuryl)-5-fluorouracil (Anai et al., *Oncology* 45(3):144-7, 1988), 1-(2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)-5-fluorouracil (Suzuko et al., *Mol. Pharmacol.* 31(3):301-6, 1987), doxifluridine (Matuura et al., *Oyo Yakuri* 29(5):803-31, 1985), 5'-deoxy-5-fluorouridine (Bollag & Hartmann, *Eur. J. Cancer* 16(4):427-32, 1980), 1-acetyl-3-O-toluyl-5-fluorouracil (Okada, *Hiroshima J. Med. Sci.* 28(1):49-66, 1979), 5-fluorouracil-m-formylbenzene-sulfonate (JP 55059173), N'-(2-furanidyl)-5-fluorouracil (JP 53149985) and 1-(2-tetrahydrofuryl)-5-fluorouracil (JP 52089680); 4'-epidoxorubicin (Lanius, Adv. Chemother. Gastrointest. Cancer, (Int. Symp.), 159-67, 1984); N-substituted deacetylvinblastine amide (vindesine) sulfates (Conrad et al., *J. Med. Chem.* 22(4):391-400, 1979); and Cu(II)-VP-16 (etoposide) complex (Tawa et al., *Bioorg. Med. Chem.* 6(7):1003-1008, 1998), pyrrolecarboxamidino-bearing etoposide analogues (Ji et al., *Bioorg. Med. Chem. Lett.* 7(5):607-612, 1997), 4β-amino etoposide analogues (Hu, University of North Carolina Dissertation, 1992), γ-lactone ring-modified arylamino etoposide analogues (Zhou et al., *J. Med. Chem.* 37(2):287-92, 1994), N-glucosyl etoposide analogue (Allevi et al., *Tetrahedron Lett.* 34(45):7313-16, 1993), etoposide A-ring analogues (Kadow et al., *Bioorg. Med. Chem. Lett.* 2(1):17-22, 1992), 4'-deshydroxy-4'-methyl etoposide (Saulnier et al., *Bioorg. Med. Chem. Lett.* 2(10):1213-18, 1992), pendulum ring etoposide analogues (Sinha et al., *Eur. J. Cancer* 26(5):590-3, 1990) and E-ring desoxy etoposide analogues (Saulnier et al., *J. Med. Chem.* 32(7):1418-20, 1989).

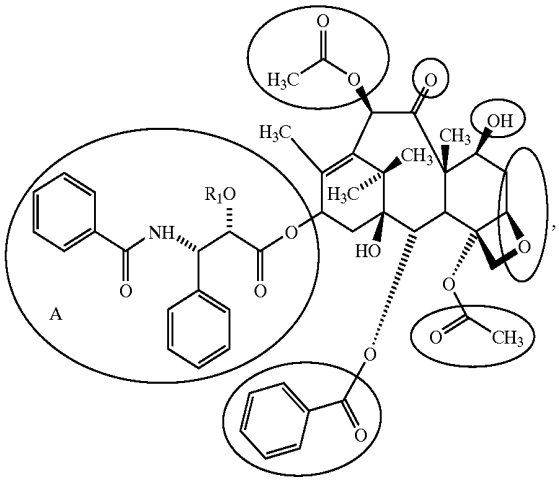
[**0183**] Within one preferred embodiment of the invention, the cell cycle inhibitor is paclitaxel, a compound which disrupts mitosis (M-phase) by binding to tubulin to form abnormal mitotic spindles or an analogue or derivative thereof. Briefly, paclitaxel is a highly derivatized diterpenoid (Wani et al., *J. Am. Chem. Soc.* 93:2325, 1971) which has been obtained from the harvested and dried bark of *Taxus brevifolia* (Pacific Yew) and *Taxomyces Andreanae and Endophytic Fungus* of the Pacific Yew (Stierle et al., *Science* 60:214-216, 1993). "Paclitaxel" (which should be understood herein to include formulations, prodrugs, analogues and derivatives such as, for example, TAXOL (Bristol Myers Squibb, New York, N.Y., TAXOTERE (Aventis Pharmaceuticals, France), docetaxel, 10-desacetyl analogues of paclitaxel and 3'N-desbenzoyl-3'N-t-butoxy carbonyl analogues of paclitaxel) may be readily prepared utilizing techniques known to those skilled in the art (see, e.g., Schiff et al., *Nature* 277:665-667, 1979; Long and Fairchild, *Cancer Research* 54:4355-4361, 1994; Ringel and Horwitz, J. Natl Cancer Inst. 83(4):288-291; 1991; Pazdur et al., *Cancer Treat. Rev.* 19(4):351-386, 1993; WO 94/07882; WO 94/07881; WO 94/07880; WO 94/07876; WO 93/23555; WO 93/10076; WO94/00156; WO 93/24476; EP 590267; WO 94/20089; U.S. Pat. Nos. 5,294,637; 5,283,253; 5,279,949; 5,274,137; 5,202,448; 5,200,534; 5,229,529; 5,254,580; 5,412,092; 5,395,850; 5,380,751; 5,350,866; 4,857,653; 5,272,171; 5,411,984; 5,248,796; 5,248,796; 5,422,364; 5,300,638; 5,294,637; 5,362,831; 5,440,056; 4,814,470; 5,278,324; 5,352,805; 5,411,984; 5,059,699; 4,942,

184; Tetrahedron Letters 35(52):9709-9712, 1994; *J. Med. Chem.* 35:4230-4237, 1992; *J. Med. Chem.* 34:992-998, 1991; *J. Natural Prod.* 57(10):1404-1410, 1994; *J. Natural Prod.* 57(11):1580-1583, 1994; *J. Am. Chem. Soc.* 110:6558-6560, 1988), or obtained from a variety of commercial sources, including for example, Sigma Chemical Co., St. Louis, Mo. (T7402—from *Taxus brevifolia*).

[**0184**] Representative examples of paclitaxel derivatives or analogues include 7-deoxy-docetaxol, 7,8-cyclopropataxanes, N-substituted 2-azetidones, 6,7-epoxy paclitaxels, 6,7-modified paclitaxels, 10-desacetoxytaxol, 10-deacetyltaxol (from 10-deacetylbaccatin III), phosphonooxy and carbonate derivatives of taxol, taxol 2',7-di(sodium 1,2-benzenedicarboxylate, 10-desacetoxy-11,12-dihydrotaxol-10, 12(18)-diene derivatives, 10-desacetoxytaxol, Protaxol (2'-and/or 7-O-ester derivatives), (2'-and/or 7-O-carbonate derivatives), asymmetric synthesis of taxol side chain, fluoro taxols, 9-deoxotaxane, (13-acetyl-9-deoxobaccatine III, 9-deoxotaxol, 7-deoxy-9-deoxotaxol, 10-desacetoxy-7-deoxy-9-deoxotaxol, Derivatives containing hydrogen or acetyl group and a hydroxy and tert-butoxycarbonylamino, sulfonated 2'-acryloyltaxol and sulfonated 2'-O-acyl acid taxol derivatives, succinyltaxol, 2'-γ-aminobutyryltaxol formate, 2'-acetyl taxol, 7-acetyl taxol, 7-glycine carbamate taxol, 2'-OH-7-PEG(5000) carbamate taxol, 2'-benzoyl and 2',7-dibenzoyl taxol derivatives, other prodrugs (2'-acetyltaxol; 2',7-diacetyltaxol; 2'succinyltaxol; 2'-(beta-alanyl)-taxol); 2'gamma-aminobutyryltaxol formate; ethylene glycol derivatives of 2'-succinyltaxol; 2'-glutaryltaxol; 2'-(N,N-dimethylglycyl) taxol; 2'-(2-(N,N-dimethylamino)propionyl)taxol; 2'orthocarboxybenzoyl taxol; 2'aliphatic carboxylic acid derivatives of taxol, Prodrugs {2'(N,N-diethylaminopropionyl)taxol, 2'(N,N-dimethylglycyl)taxol, 7(N,N-dimethylglycyl)taxol, 2',7-di-(N, N-dimethylglycyl)taxol, 7(N,N-diethylaminopropionyl)taxol, 2',7-di(N,N-diethylaminopropionyl)taxol, 2'-(L-glycyl)taxol, 7-(L-glycyl)taxol, 2',7-di(L-glycyl)taxol, 2'-(L-alanyl)taxol, 7-(L-alanyl)taxol, 2',7-di(L-alanyl)taxol, 2'-(L-leucyl)taxol, 7-(L-leucyl)taxol, 2',7-di(L-leucyl)taxol, 2'-(L-isoleucyl-)taxol, 7-(L-isoleucyl)taxol, 2',7-di(L-isoleucyl)taxol, 2'-(L-valyl)taxol, 7-(L-valyl)taxol, 2',7-di(L-valyl)taxol, 2'-(L-phenylalanyl)taxol, 7-(L-phenylalanyl)taxol, 2',7-di(L-phenylalanyl)taxol, 2'-(L-prolyl)taxol, 7-(L-prolyl)taxol, 2',7-di(L-prolyl)taxol, 2'-(L-lysyl)taxol, 7-(L-lysyl)taxol, 2',7-di(L-lysyl)taxol, 2'-(L-glutamyl)taxol, 7-(L-glutamyl-)taxol, 2',7-di(L-glutamyl)taxol, 2'-(L-arginyl)taxol, 7-(L-arginyl)taxol, 2',7-di(L-arginyl)taxol}, taxol analogues with modified phenylisoserine side chains, TAXOTERE, (N-debenzoyl-N-tert-(butoxycaronyl)-10-deacetyltaxol, and taxanes (e.g., baccatin III, cephalomannine, 10-deacetylbaccatin III, brevifoliol, yunantaxusin and taxusin); and other taxane analogues and derivatives, including 14-beta-hydroxy-10 deacetybaccatin III, debenzoyl-2-acyl paclitaxel derivatives, benzoate paclitaxel derivatives, phosphonooxy and carbonate paclitaxel derivatives, sulfonated 2'-acryloyltaxol; sulfonated 2'-O-acyl acid paclitaxel derivatives, 18-site-substituted paclitaxel derivatives, chlorinated paclitaxel analogues, C4 methoxy ether paclitaxel derivatives, sulfenamide taxane derivatives, brominated paclitaxel analogues, Girard taxane derivatives, nitrophenyl paclitaxel, 10-deacetylated substituted paclitaxel derivatives, 14-beta-hydroxy-10 deacetylbaccatin III taxane derivatives, C7 taxane derivatives, C10 taxane derivatives, 2-debenzoyl-2-acyl taxane derivatives, 2-debenzoyl and -2-acyl paclitaxel derivatives, taxane and baccatin III analogues bearing new C2 and C4 functional groups, n-acyl paclitaxel analogues, 10-deacetylbaccatin III and 7-protected-10-deacetylbaccatin III derivatives from 10-deacetyl taxol A, 10-deacetyl taxol B, and 10-deacetyl taxol, benzoate derivatives of taxol, 2-aroyl-4-acyl paclitaxel analogues, orthro-ester paclitaxel analogues, 2-aroyl-4-acyl paclitaxel analogues and 1-deoxy paclitaxel and 1-deoxy paclitaxel analogues.

[**0185**] In one aspect, the cell cycle inhibitor is a taxane having the formula (C1):

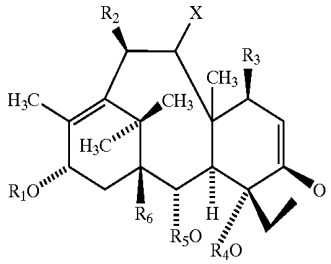
(C1)



[**0186**] where the gray-highlighted portions may be substituted and the non-highlighted portion is the taxane core. A side-chain (labeled "A" in the diagram) is desirably present in order for the compound to have good activity as a cell cycle inhibitor. Examples of compounds having this structure include paclitaxel (Merck Index entry 7117), docetaxol (TAXOTERE, Merck Index entry 3458), and 3'-desphenyl-3'-(4-ntirophenyl)-N-debenzoyl-N-(t-butoxycarbonyl)-10-deacetyltaxol.

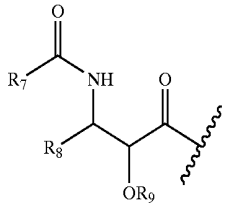
[**0187**] In one aspect, suitable taxanes such as paclitaxel and its analogues and derivatives are disclosed in U.S. Pat. No. 5,440,056 as having the structure (C2):

(C2)



[**0188**] wherein X may be oxygen (paclitaxel), hydrogen (9-deoxy derivatives), thioacyl, or dihydroxyl precursors; R_1 is selected from paclitaxel or TAXOTERE side chains or alkanoyl of the formula (C3)

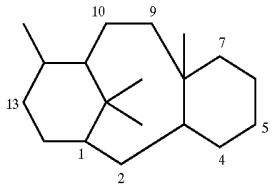
(C3)



[0189] wherein R_7 is selected from hydrogen, alkyl, phenyl, alkoxy, amino, phenoxy (substituted or unsubstituted); R_8 is selected from hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, phenyl (substituted or unsubstituted), alpha or beta-naphthyl; and R_9 is selected from hydrogen, alkanoyl, substituted alkanoyl, and aminoalkanoyl; where substitutions refer to hydroxyl, sulfhydryl, allalkoxyl, carboxyl, halogen, thioalkoxyl, N,N-dimethylamino, alkylamino, dialkylamino, nitro, and —OSO_3H, and/or may refer to groups containing such substitutions; R_2 is selected from hydrogen or oxygen-containing groups, such as hydrogen, hydroxyl, alkoyl, alkanoyloxy, aminoalkanoyloxy, and peptidyalkanoyloxy; R_3 is selected from hydrogen or oxygen-containing groups, such as hydrogen, hydroxyl, alkoyl, alkanoyloxy, aminoalkanoyloxy, and peptidyalkanoyloxy, and may further be a silyl containing group or a sulphur containing group; R_4 is selected from acyl, alkyl, alkanoyl, aminoalkanoyl, peptidylalkanoyl and aroyl; R_5 is selected from acyl, alkyl, alkanoyl, aminoalkanoyl, peptidylalkanoyl and aroyl; R_6 is selected from hydrogen or oxygen-containing groups, such as hydrogen, hydroxyl alkoyl, alkanoyloxy, aminoalkanoyloxy, and peptidyalkanoyloxy.

[0190] In one aspect, the paclitaxel analogues and derivatives useful as cell cycle inhibitors are disclosed in PCT International Patent Application No. WO 93/10076. As disclosed in this publication, the analogue or derivative should have a side chain attached to the taxane nucleus at C_{13}, as shown in the structure below (formula C4), in order to confer antitumor activity to the taxane.

(C4)



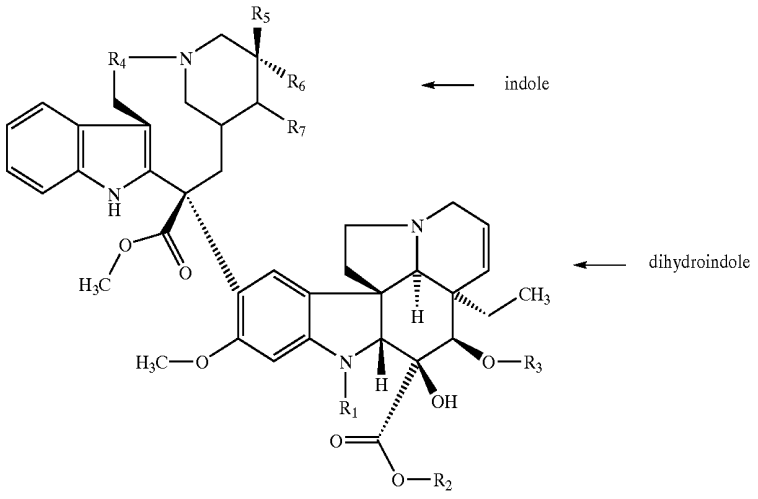
[0191] WO 93/10076 discloses that the taxane nucleus may be substituted at any position with the exception of the existing methyl groups. The substitutions may include, for example, hydrogen, alkanoyloxy, alkenoyloxy, aryloyloxy. In addition, oxo groups may be attached to carbons labeled 2, 4, 9, and/or 10. As well, an oxetane ring may be attached at carbons 4 and 5. As well, an oxirane ring may be attached to the carbon labeled 4.

[0192] In one aspect, the taxane-based cell cycle inhibitor useful in the present invention is disclosed in U.S. Pat. No. 5,440,056, which discloses 9-deoxo taxanes. These are compounds lacking an oxo group at the carbon labeled 9 in the taxane structure shown above (formula C4). The taxane ring may be substituted at the carbons labeled 1, 7 and 10 (independently) with H, OH, O—R, or O—CO—R where R is an alkyl or an aminoalkyl. As well, it may be substituted at carbons labeled 2 and 4 (independently) with aryol, alkanoyl, aminoalkanoyl or alkyl groups. The side chain of formula (C3) may be substituted at R_7 and R_8 (independently) with phenyl rings, substituted phenyl rings, linear alkanes/alkenes, and groups containing H, O or N. R_9 may be substituted with H, or a substituted or unsubstituted alkanoyl group.

[0193] Taxanes in general, and paclitaxel is particular, is considered to function as a cell cycle inhibitor by acting as an anti-microtubule agent, and more specifically as a stabilizer. These compounds have been shown useful in the treatment of proliferative disorders, including: non-small cell (NSC) lung; small cell lung; breast; prostate; cervical; endometrial; head and neck cancers.

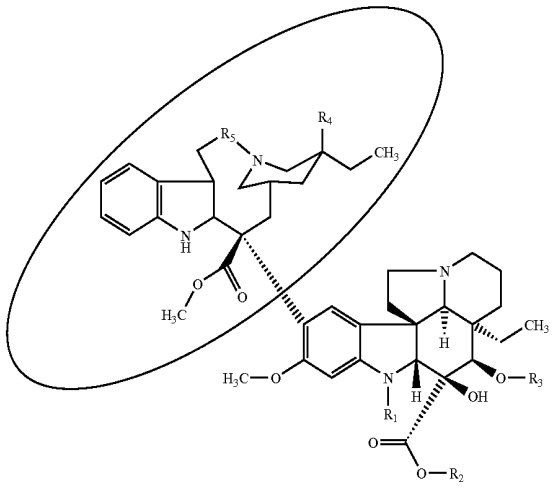
[0194] In another aspect, the anti-microtuble agent (microtubule inhibitor) is albendazole (carbamic acid, [5-(propylthio)-1H-benzimidazol-2-yl]-, methyl ester), LY-355703 (1,4-dioxa-8,11-diazacyclohexadec-13-ene-2,5,9,12-tetrone, 10-[(3-chloro-4-methoxyphenyl)methyl]-6,6-dimethyl-3-(2-methylpropyl)-16-[(1S)-1-[(2S,3R)-3-phenyloxiranyl]ethyl]-, (3S,10R,13E,16S)-), vindesine (vincaleukoblastine, 3-(aminocarbonyl)-04-deacetyl-3-de(methoxycarbonyl)-), or WAY-174286

[0195] In another aspect, the cell cycle inhibitor is a vinca alkaloid. Vinca alkaloids have the following general structure. They are indole-dihydroindole dimers.



[0196] As disclosed in U.S. Pat. Nos. 4,841,045 and 5,030,620, R_1 can be a formyl or methyl group or alternately H. R_1 can also be an alkyl group or an aldehyde-substituted alkyl (e.g., CH_2CHO). R_2 is typically a CH_3 or NH_2 group. However it can be alternately substituted with a lower alkyl ester or the ester linking to the dihydroindole core may be substituted with C(O)—R where R is NH_2, an amino acid ester or a peptide ester. R_3 is typically $C(O)CH_3$, CH_3 or H. Alternately, a protein fragment may be linked by a bifunctional group, such as maleoyl amino acid. R_3 can also be substituted to form an alkyl ester which may be further substituted. R_4 may be —CH_2— or a single bond. R_5 and R_6 may be H, OH or a lower alkyl, typically —CH_2CH_3. Alternatively R_6 and R_7 may together form an oxetane ring. R_7 may alternately be H. Further substitutions include molecules wherein methyl groups are substituted with other alkyl groups, and whereby unsaturated rings may be derivatized by the addition of a side group such as an alkane, alkene, alkyne, halogen, ester, amide or amino group.

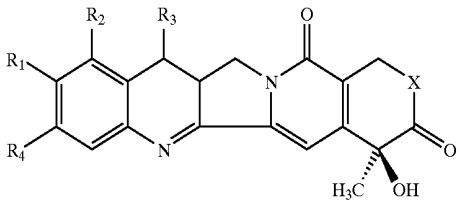
[0197] Exemplary vinca alkaloids are vinblastine, vincristine, vincristine sulfate, vindesine, and vinorelbine, having the structures:



	R_1	R_2	R_3	R_4	R_5
Vinblastine:	CH_3	CH_3	$C(O)CH_3$	OH	CH_2
Vincristine:	CH_2O	CH_3	$C(O)CH_3$	OH	CH_2
Vindesine:	CH_3	NH_2	H	OH	CH_2
Vinorelbine:	CH_3	CH_3	CH_3	H	single bond

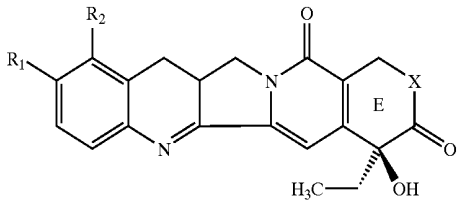
[0198] Analogues typically require the side group (shaded area) in order to have activity. These compounds are thought to act as cell cycle inhibitors by functioning as anti-microtubule agents, and more specifically to inhibit polymerization. These compounds have been shown useful in treating proliferative disorders, including NSC lung; small cell lung; breast; prostate; brain; head and neck; retinoblastoma; bladder; and penile cancers; and soft tissue sarcoma.

[0199] In another aspect, the cell cycle inhibitor is a camptothecin, or an anolog or derivative thereof. Camptothecins have the following general structure.



[0200] In this structure, X is typically O, but can be other groups, e.g., NH in the case of 21-lactam derivatives. R, is typically H or OH, but may be other groups, e.g., a terminally hydroxylated C_{1-3} alkane. R_2 is typically H or an amino containing group such as $(CH_3)_2NHCH_2$, but may be other groups e.g., NO_2, NH_2, halogen (as disclosed in, e.g., U.S. Pat. No. 5,552,156) or a short alkane containing these groups. R_3 is typically H or a short alkyl such as C_2H_5. R_4 is typically H but may be other groups, e.g., a methylenedioxy group with R_1.

[0201] Exemplary camptothecin compounds include topotecan, irinotecan (CPT-11), 9-aminocamptothecin, 21-lactam-20(S)-camptothecin, 10,11-methylenedioxycamptothecin, SN-38, 9-nitrocamptothecin, 10-hydroxycamptothecin. Exemplary compounds have the structures:



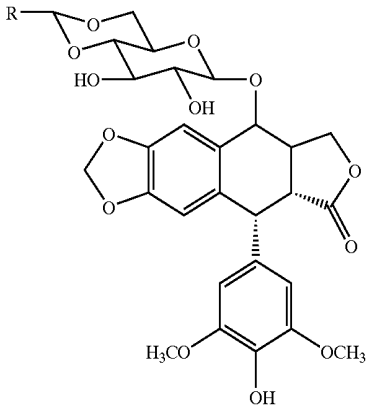
	R_1	R_2	R_3
Camptothecin:	H	H	H
Topotecan:	OH	$(CH_3)_2NHCH_2$	H
SN-38:	OH	H	C_2H_5

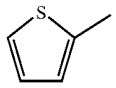
X: O for most analogs, NH for 21-lactam analogs

[0202] Camptothecins have the five rings shown here. The ring labeled E must be intact (the lactone rather than carboxylate form) for maximum activity and minimum toxicity. These compounds are useful to as cell cycle inhibitors, where they can function as topoisomerase I inhibitors and/or DNA cleavage agents. They have been shown useful in the treatment of proliferative disorders, including, for example, NSC lung; small cell lung; and cervical cancers.

[0203] In another aspect, the cell cycle inhibitor is a podophyllotoxin, or a derivative or an analogue thereof.

Exemplary compounds of this type are etoposide or teniposide, which have the following structures:

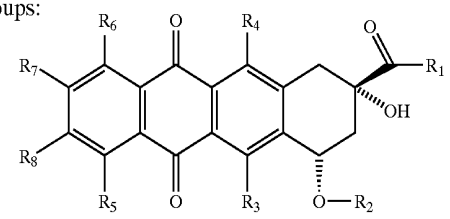


	R
Etoposide	CH_3
Teniposide	

[0204] These compounds are thought to function as cell cycle inhibitors by being topoisomerase II inhibitors and/or by DNA cleaving agents. They have been shown useful as antiproliferative agents in, e.g., small cell lung, prostate, and brain cancers, and in retinoblastoma.

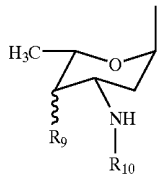
[0205] Another example of a DNA topoisomerase inhibitor is lurtotecan dihydrochloride (11H-1,4-dioxino[2,3-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-9,12(8H,14H)-dione, 8-ethyl-2,3-dihydro-8-hydroxy-15-[(4-methyl-1-piperazinyl)methyl]-, dihydrochloride, (S)-).

[0206] In another aspect, the cell cycle inhibitor is an anthracycline. Anthracyclines have the following general structure, where the R groups may be a variety of organic groups:



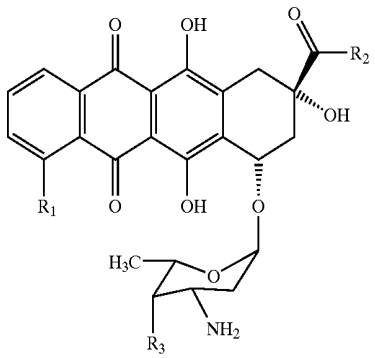
[0207] According to U.S. Pat. No. 5,594,158, suitable R groups are: R_1 is CH_3 or CH_2OH; R_2 is daunosamine or H; R_3 and R_4 are independently one of OH, NO_2, NH_2, F, Cl, Br, I, CN, H or groups derived from these; R_{5-7} are all H or R_5 and R_6 are H and R_7 and R_8 are alkyl or halogen, or vice versa: R_7 and R_8 are H and R_5 and R_6 are alkyl or halogen.

[0208] According to U.S. Pat. No. 5,843,903, R_2 may be a conjugated peptide. According to U.S. Pat. Nos. 4,215,062 and 4,296,105, R_5 may be OH or an ether linked alkyl group. R_1 may also be linked to the anthracycline ring by a group other than C(O), such as an alkyl or branched alkyl group having the C(O) linking moiety at its end, such as —$CH_2CH(CH_2$—X)C(O)—R_1, wherein X is H or an alkyl group (see, e.g., U.S. Pat. No. 4,215,062). R_2 may alternately be a group linked by the functional group =N—NHC(O)—Y, where Y is a group such as a phenyl or substituted phenyl ring. Alternately R_3 may have the following structure:

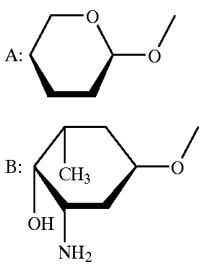


[0209] in which R_9 is OH either in or out of the plane of the ring, or is a second sugar moiety such as R_3. R_{10} may be H or form a secondary amine with a group such as an aromatic group, saturated or partially saturated 5 or 6 membered heterocyclic having at least one ring nitrogen (see U.S. Pat. No. 5,843,903). Alternately, R_{10} may be derived from an amino acid, having the structure —C(O)CH(NHR_{11})(R_{12}), in which R_{11} is H, or forms a C_{3-4} membered alkylene with R_{12}. R_{12} may be H, alkyl, aminoalkyl, amino, hydroxy, mercapto, phenyl, benzyl or methylthio (see U.S. Pat. No. 4,296,105).

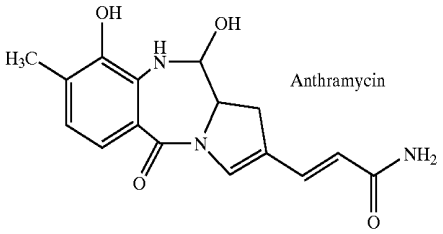
[0210] Exemplary anthracyclines are doxorubicin, daunorubicin, idarubicin, epirubicin, pirarubicin, zorubicin, and carubicin. Suitable compounds have the structures:



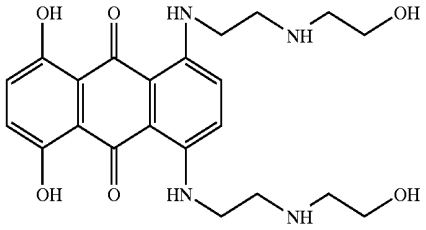
	R_1	R_2	R_3
Doxorubicin:	OCH_3	CH_2OH	OH out of ring plane
Epirubicin: (4' epimer of doxorubicin)	OCH_3	CH_2OH	OH in ring plane
Daunorubicin:	OCH_3	CH_3	OH out of ring plane
Idarubicin:	H	CH_3	OH out of ring plane
Pirarubicin:	OCH_3	OH	A
Zorubicin:	OCH_3	=N—NHC(O)C_2H_5	B
Carubicin:	OH	CH_3	B



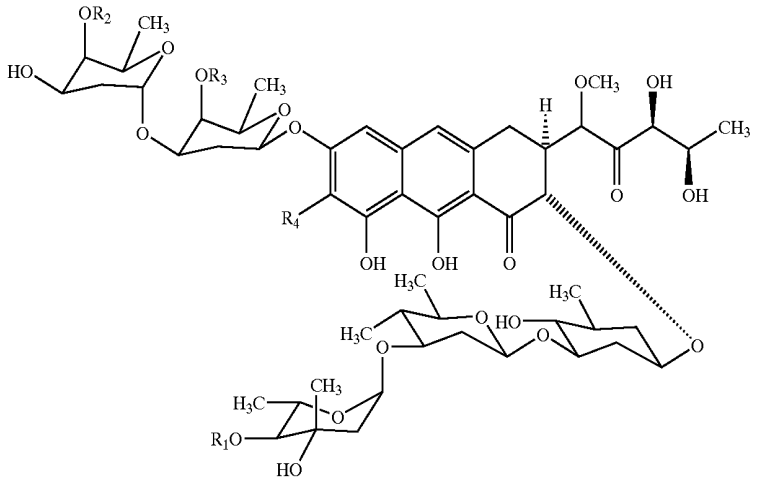
[0211] Other suitable anthracyclines are anthramycin, mitoxantrone, menogaril, nogalamycin, aclacinomycin A, olivomycin A, chromomycin A_3, and plicamycin having the structures:



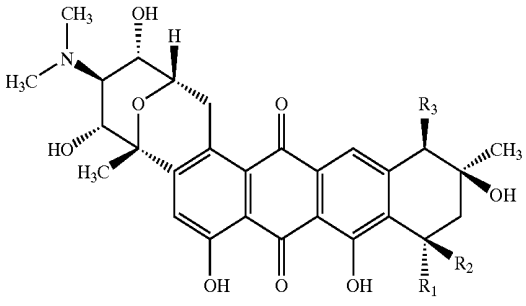
Anthramycin



Mitoxantrone



	R_1	R_2	R_3	R_4
Olivomycin A	$COCH(CH_3)_2$	CH_3	$COCH_3$	H
Chromomycin A_3	$COCH_3$	CH_3	$COCH_3$	CH_3
Plicamycin	H	H	H	CH_3



	R_1	R_2	R_3
Menogaril	H	OCH_3	H
Nogalamycin	O-sugar	H	$COOCH_3$

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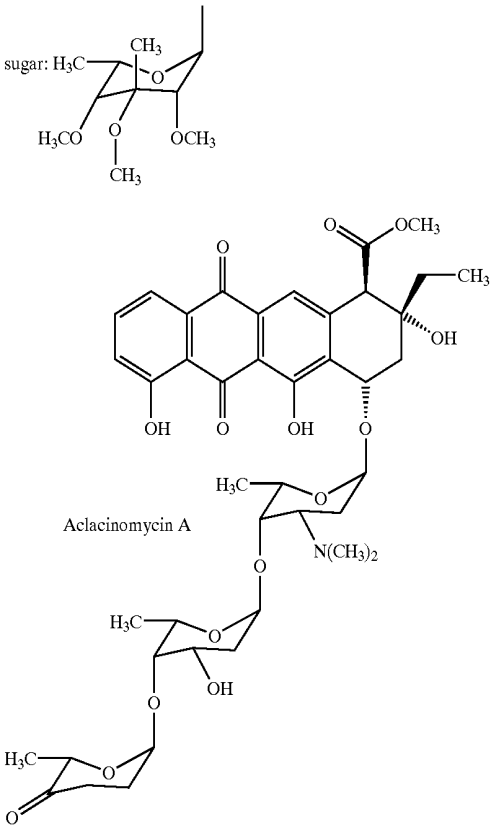
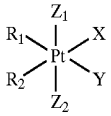


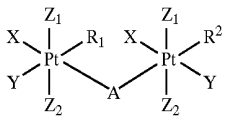
[0212] These compounds are thought to function as cell cycle inhibitors by being topoisomerase inhibitors and/or by DNA cleaving agents. They have been shown useful in the treatment of proliferative disorders, including small cell lung; breast; endometrial; head and neck; retinoblastoma; liver; bile duct; islet cell; and bladder cancers; and soft tissue sarcoma.

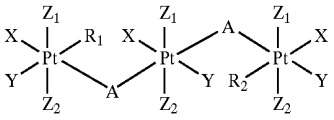
[0213] In another aspect, the cell cycle inhibitor is a platinum compound. In general, suitable platinum complexes may be of Pt(II) or Pt(IV) and have this basic structure:

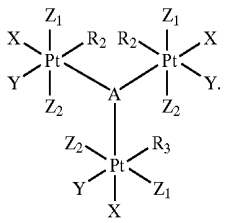


[0214] wherein X and Y are anionic leaving groups such as sulfate, phosphate, carboxylate, and halogen; R_1 and R_2 are alkyl, amine, amino alkyl any may be further substituted, and are basically inert or bridging groups. For Pt(II) complexes Z_1 and Z_2 are non-existent. For Pt(IV) Z_1 and Z_2 may be anionic groups such as halogen, hydroxy, carboxylate, ester, sulfate or phosphate. See, e.g., U.S. Pat. Nos. 4,588,831 and 4,250,189.

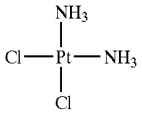
[0215] Suitable platinum complexes may contain multiple Pt atoms. See, e.g., U.S. Pat. Nos. 5,409,915 and 5,380,897. For example bisplatinum and triplatinum complexes of the type:



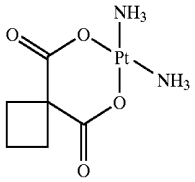




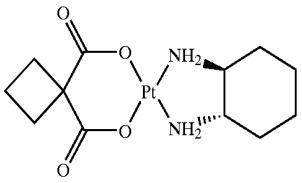
[0216] Exemplary platinum compounds are cisplatin, carboplatin, oxaliplatin, and miboplatin having the structures:



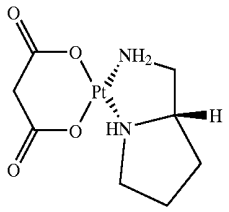
Cisplatin



Carboplatin



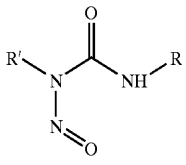
Oxaliplatin



Miboplatin

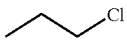
[0217] These compounds are thought to function as cell cycle inhibitors by binding to DNA, i.e., acting as alkylating agents of DNA. These compounds have been shown useful in the treatment of cell proliferative disorders, including, e.g., NSC lung; small cell lung; breast; cervical; brain; head and neck; esophageal; retinoblastom; liver; bile duct; bladder; penile; and vulvar cancers; and soft tissue sarcoma.

[0218] In another aspect, the cell cycle inhibitor is a nitrosourea. Nitrosourease have the following general structure (C5), where typical R groups are shown below.

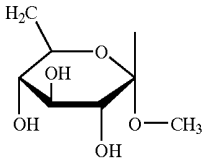


(C5)

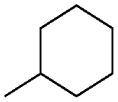
[0219] R Group:



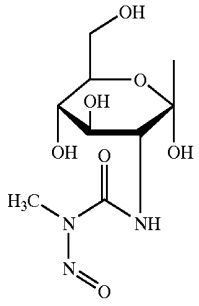
Carmustine



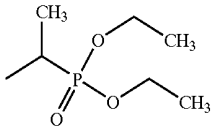
Ranimustine



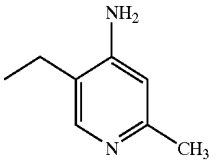
Lomustine



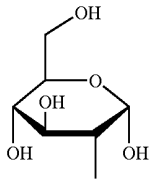
Streptozocin



Fotemustine



Nimustine



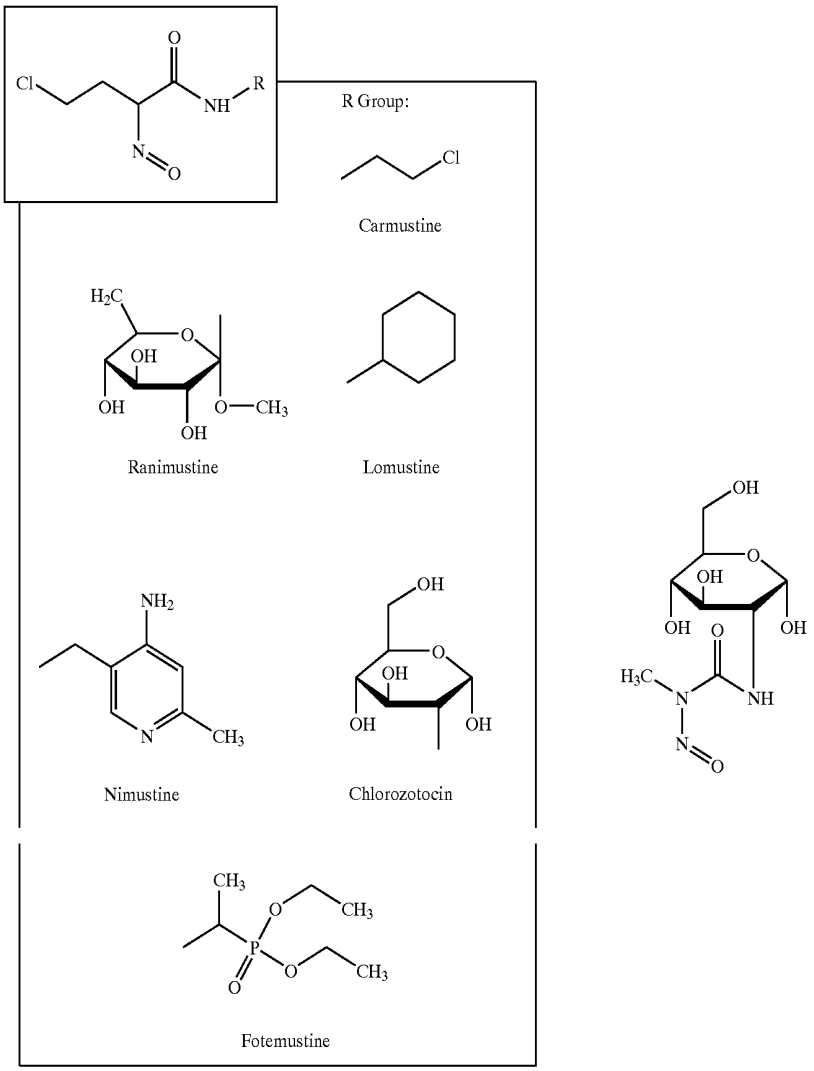
Chlorozotocin

[0220] Other suitable R groups include cyclic alkanes, alkanes, halogen substituted groups, sugars, aryl and heteroaryl groups, phosphonyl and sulfonyl groups. As disclosed in U.S. Pat. No. 4,367,239, R may suitably be CH_2—C(X)(Y)(Z), wherein X and Y may be the same or different members of the following groups: phenyl, cyclyhexyl, or a phenyl or cyclohexyl group substituted with groups such as halogen, lower alkyl (C_{1-4}), trifluore methyl, cyano, phenyl, cyclohexyl, lower alkyloxy (C_{1-4}). Z has the

following structure: -alkylene-N—R_1R_2, where R_1 and R_2 may be the same or different members of the following group: lower alkyl (C_{1-4}) and benzyl, or together R_1 and R_2 may form a saturated 5 or 6 membered heterocyclic such as pyrrolidine, piperidine, morfoline, thiomorfoline, N-lower alkyl piperazine, where the heterocyclic may be optionally substituted with lower alkyl groups.

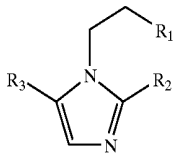
[**0221**] As disclosed in U.S. Pat. No. 6,096,923, R and R' of formula (C5) may be the same or different, where each may be a substituted or unsubstituted hydrocarbon having 1-10 carbons. Substitutions may include hydrocarbyl, halo, ester, amide, carboxylic acid, ether, thioether and alcohol groups. As disclosed in U.S. Pat. No. 4,472,379, R of formula (C5) may be an amide bond and a pyranose structure (e.g., methyl 2'-(N-(N-(2-chloroethyl)-N-nitroso-carbamoyl)-glycyl)amino-2'-deoxy-α-D-glucopyranoside). As disclosed in U.S. Pat. No. 4,150,146, R of formula (C5) may be an alkyl group of 2 to 6 carbons and may be substituted with an ester, sulfonyl, or hydroxyl group. It may also be substituted with a carboxylic acid or $CONH_2$ group.

[**0222**] Exemplary nitrosoureas are BCNU (carmustine), methyl-CCNU (semustine), CCNU (lomustine), ranimustine, nimustine, chlorozotocin, fotemustine, and streptozocin, having the structures:



[0223] These nitrosourea compounds are thought to function as cell cycle inhibitors by binding to DNA, that is, by functioning as DNA alkylating agents. These cell cycle inhibitors have been shown useful in treating cell proliferative disorders such as, for example, islet cell; small cell lung; melanoma; and brain cancers.

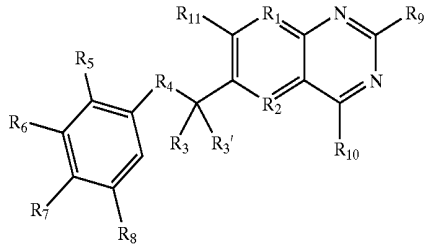
[0224] In another aspect, the cell cycle inhibitor is a nitroimidazole, where exemplary nitroimidazoles are metronidazole, benznidazole, etanidazole, and misonidazole, having the structures:



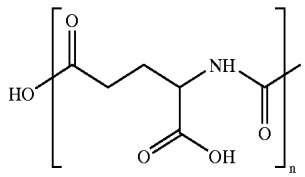
	R_1	R_2	R_3
Metronidazoled	OH	CH_3	NO_2
Benznidazole	$C(O)NHCH_2$-benzyl	NO_2	H
Etanidazole	$CONHCH_2CH_2OH$	NO_2	H

[0225] Suitable nitroimidazole compounds are disclosed in, e.g., U.S. Pat. Nos. 4,371,540 and 4,462,992.

[0226] In another aspect, the cell cycle inhibitor is a folic acid antagonist, such as methotrexate or derivatives or analogues thereof, including edatrexate, trimetrexate, raltitrexed, piritrexim, denopterin, tomudex, and pteropterin. Methotrexate analogues have the following general structure:

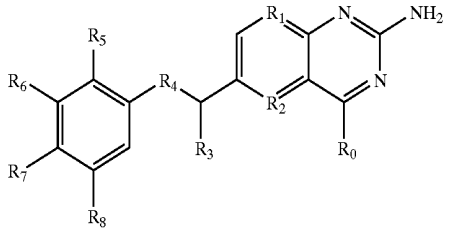


[0227] The identity of the R group may be selected from organic groups, particularly those groups set forth in U.S. Pat. Nos. 5,166,149 and 5,382,582. For example, R_1 may be N, R_2 may be N or $C(CH_3)$, R_3 and R_3' may H or alkyl, e.g., CH_3, R_4 may be a single bond or NR, where R is H or alkyl group. $R_{5,6,8}$ may be H, OCH_3, or alternately they can be halogens or hydro groups. R_7 is a side chain of the general structure:

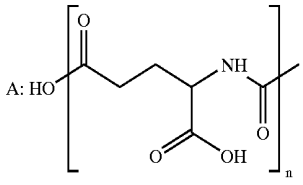


[0228] wherein n=1 for methotrexate, n=3 for pteropterin. The carboxyl groups in the side chain may be esterified or form a salt such as a Zn^{2+} salt. R_9 and R_{10} can be NH_2 or may be alkyl substituted.

[0229] Exemplary folic acid antagonist compounds have the structures:



	R_0	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
Methotrexate	NH_2	N	N	H	$N(CH_3)$	H	H	A (n = 1)	H
Edatrexate	NH_2	N	N	H	$N(CH_2CH_3)$	H	H	A (n = 1)	H
Trimetrexate	NH_2	N	$C(CH_3)$	H	NH	H	OCH_3	OCH_3	OCH_3
Pteropterin	NH_2	N	N	H	$N(CH_3)$	H	H	A (n = 1)	H
Denopterin	OH	N	N	CH_3	$N(CH_3)$	H	H	A (n = 1)	H
Piritrexin	NH_2	N	$C(CH_3)H$	single bond	OCH_3	H	H	OCH_3	H



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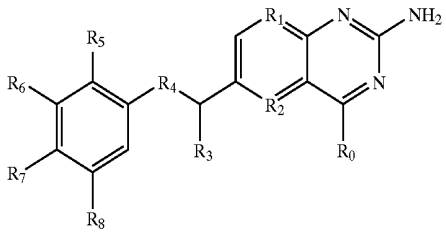
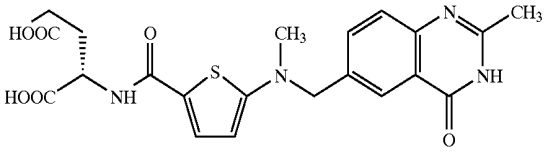


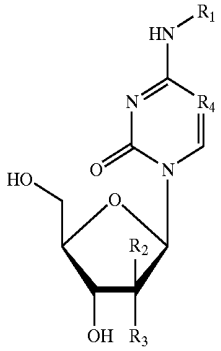
R_0	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8



Tomudex

[0230] These compounds are thought to function as cell cycle inhibitors by serving as antimetabolites of folic acid. They have been shown useful in the treatment of cell proliferative disorders including, for example, soft tissue sarcoma, small cell lung, breast, brain, head and neck, bladder, and penile cancers.

[0231] In another aspect, the cell cycle inhibitor is a cytidine analogue, such as cytarabine or derivatives or analogues thereof, including enocitabine, FMdC ((E(−2'-deoxy-2'-(fluoromethylene)cytidine), gemcitabine, 5-azacitidine, ancitabine, and 6-azauridine. Exemplary compounds have the structures:



	R_1	R_2	R_3	R_4
Cytarabine	H	OH	H	CH
Enocitabine	$C(O)(CH_2)_{20}CH_3$	OH	H	CH
Gemcitabine	H	F	F	CH

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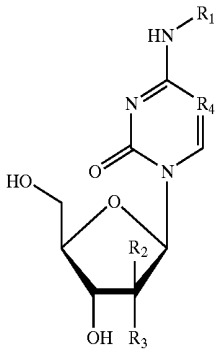
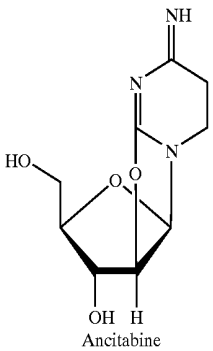


	R_1	R_2	R_3	R_4
Azacitadine	H	H	OH	N
FMdC	H	CH_2F	H	CH



Ancitabine

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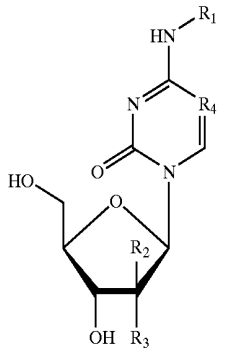
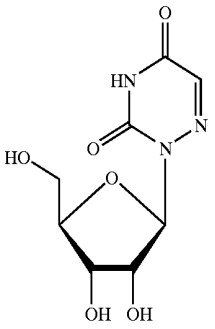
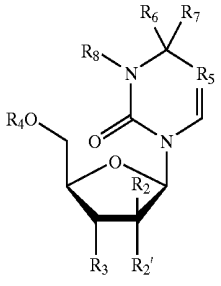


R_1	R_2	R_3	R_4

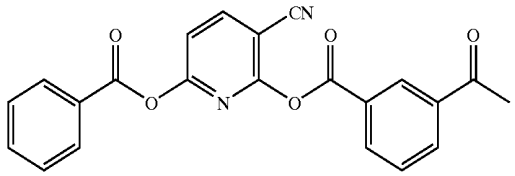


[0232] These compounds are thought to function as cell cycle inhibitors as acting as antimetabolites of pyrimidine. These compounds have been shown useful in the treatment of cell proliferative disorders including, for example, pancreatic, breast, cervical, NSC lung, and bile duct cancers.

[0233] In another aspect, the cell cycle inhibitor is a pyrimidine analogue. In one aspect, the pyrimidine analogues have the general structure:

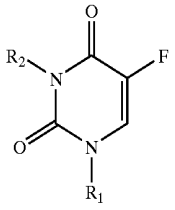


[0234] wherein positions 2', 3' and 5' on the sugar ring (R_2, R_3 and R_4, respectively) can be H, hydroxyl, phosphoryl (see, e.g., U.S. Pat. No. 4,086,417) or ester (see, e.g., U.S. Pat. No. 3,894,000). Esters can be of alkyl, cycloalkyl, aryl or heterocyclo/aryl types. The 2' carbon can be hydroxylated at either R_2 or R_2', the other group is H. Alternately, the 2' carbon can be substituted with halogens e.g., fluoro or difluoro cytidines such as Gemcytabine. Alternately, the sugar can be substituted for another heterocyclic group such as a furyl group or for an alkane, an alkyl ether or an amide linked alkane such as $C(O)NH(CH_2)_5CH_3$. The 20 amine can be substituted with an aliphatic acyl (R_1) linked with an amide (see, e.g., U.S. Pat. No. 3,991,045) or urethane (see, e.g., U.S. Pat. No. 3,894,000) bond. It can also be further substituted to form a quaternary ammonium salt. R_5 in the pyrimidine ring may be N or CR, where R is H, halogen containing groups, or alkyl (see, e.g., U.S. Pat. No. 4,086,417). R_8 and R_7 can together can form an oxo group or R_6=—NH—R, and R_7=H. R_8 is H or R_7 and R_8 together can form a double bond or R_8 can be X, where X is:

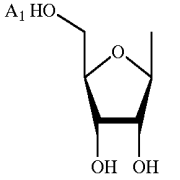


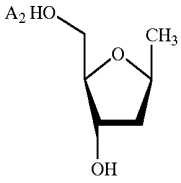
[0235] Specific pyrimidine analogues are disclosed in U.S. Pat. No. 3,894,000 (see, e.g., 2'-O-palmityl-ara-cytidine, 3'-O-benzoyl-ara-cytidine, and more than 10 other examples); U.S. Pat. No. 3,991,045 (see, e.g., N4-acyl-1-β-D-arabinofuranosylcytosine, and numerous acyl groups derivatives as listed therein, such as palmitoyl.

[0236] In another aspect, the cell cycle inhibitor is a fluoropyrimidine analogue, such as 5-fluorouracil, or an analogue or derivative thereof, including carmofur, doxifluridine, emitefur, tegafur, and floxuridine. Exemplary compounds have the structures:



	R_1	R_2
5-Fluorouracil	H	H
Carmofur	$C(O)NH(CH_2)_5CH_3$	H
Doxifluridine	A_1	H
Floxuridine	A_2	H
Emitefur	$CH_2OCH_2CH_3$	B
Tegafur		H





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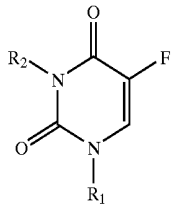
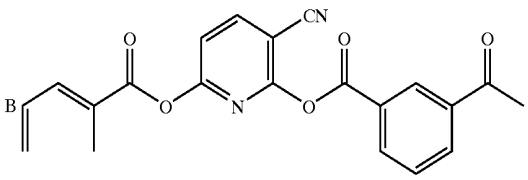
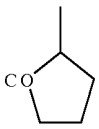
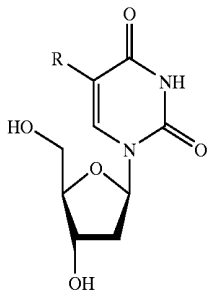






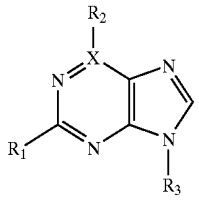
[0237] Other suitable fluoropyrimidine analogues include 5-FudR (5-fluoro-deoxyuridine), or an analogue or derivative thereof, including 5-iododeoxyuridine (5-IudR), 5-bromodeoxyuridine (5-BudR), fluorouridine triphosphate (5-FUTP), and fluorodeoxyuridine monophosphate (5-dFUMP). Exemplary compounds have the structures:



5-Fluoro-2'-deoxyuridine: R = F
5-Bromo-2'-deoxyuridine: R = Br
5-Iodoo-2'-deoxyuridine: R = I

[0238] These compounds are thought to function as cell cycle inhibitors by serving as antimetabolites of pyrimidine. These compounds have been shown useful in the treatment of cell proliferative disorders such as breast, cervical, non-melanoma skin, head and neck, esophageal, bile duct, pancreatic, islet cell, penile, and vulvar cancers.

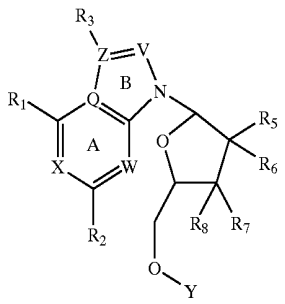
[0239] In another aspect, the cell cycle inhibitor is a purine analogue. Purine analogues have the following general structure.



[0240] wherein X is typically carbon; R_1 is H, halogen, amine or a substituted phenyl; R_2 is H, a primary, secondary or tertiary amine, a sulfur containing group, typically —SH, an alkane, a cyclic alkane, a heterocyclic or a sugar; R_3 is H, a sugar (typically a furanose or pyranose structure), a substituted sugar or a cyclic or heterocyclic alkane or aryl group. See, e.g., U.S. Pat. No. 5,602,140 for compounds of this type.

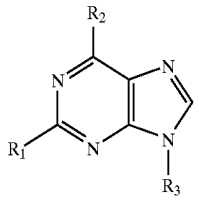
[0241] In the case of pentostatin, X—R2 is —$CH_2CH(OH)$—. In this case a second carbon atom is inserted in the ring between X and the adjacent nitrogen atom. The X—N double bond becomes a single bond.

[0242] U.S. Pat. No. 5,446,139 describes suitable purine analogues of the type shown in the formula.

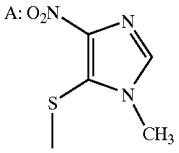


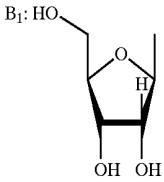
[0243] wherein N signifies nitrogen and V, W, X, Z can be either carbon or nitrogen with the following provisos. Ring A may have 0 to 3 nitrogen atoms in its structure. If two nitrogens are present in ring A, one must be in the W position. If only one is present, it must not be in the Q position. V and Q must not be simultaneously nitrogen. Z and Q must not be simultaneously nitrogen. If Z is nitrogen, R_3 is not present. Furthermore, R_{13} are independently one of H, halogen, C_{1-7} alkyl, C_{1-7} alkenyl, hydroxyl, mercapto, C_{1-7} alkylthio, C_{1-7} alkoxy, C_{2-7} alkenyloxy, aryl oxy, nitro, primary, secondary or tertiary amine containing group. R_{5-8} are H or up to two of the positions may contain independently one of OH, halogen, cyano, azido, substituted amino, R_5 and R_7 can together form a double bond. Y is H, a C_{1-7} alkylcarbonyl, or a mono- di or tri phosphate.

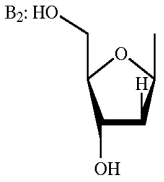
[0244] Exemplary suitable purine analogues include 6-mercaptopurine, thiguanosine, thiamiprine, cladribine, fludaribine, tubercidin, puromycin, pentoxyfilline; where these compounds may optionally be phosphorylated. Exemplary compounds have the structures:

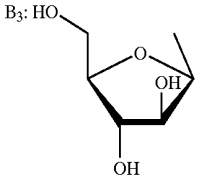


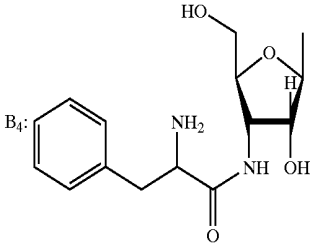
	R_1	R_2	R_3
6-Mercaptopurine	H	SH	H
Thioquanosine	NH_2	SH	B_1
Thiamiprine	NH_2	A	H
Cladtribine	Cl	NH_2	B_2
Fludarabine	F	NH_2	B_2
Purromycin	H	$N(CH_3)_2$	B_4
Tubercidin	H	NH_2	B_1











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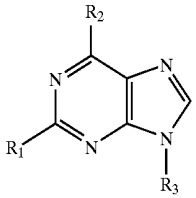
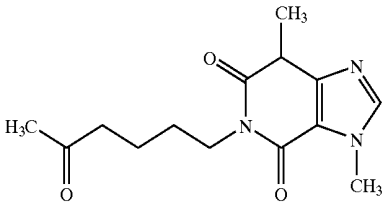


	R_1	R_2	R_3

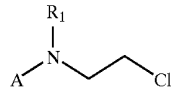


Pentoxyfilline

[0245] These compounds are thought to function as cell cycle inhibitors by serving as antimetabolites of purine.

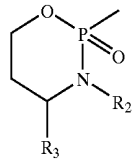
[0246] In another aspect, the cell cycle inhibitor is a nitrogen mustard. Many suitable nitrogen mustards are known and are suitably used as a cell cycle inhibitor in the present invention. Suitable nitrogen mustards are also known as cyclophosphamides.

[0247] A preferred nitrogen mustard has the general structure:



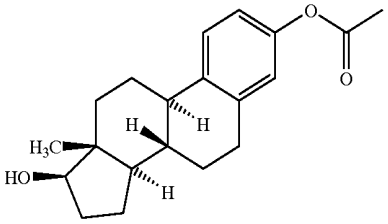
(i)

[0248] Where A is:

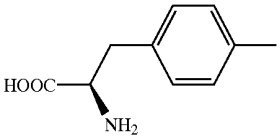


[0249] or —CH_3 or other alkane, or chloronated alkane, typically $CH_2CH(CH_3)Cl$, or a polycyclic group such as B, or a substituted phenyl such as C or a heterocyclic group such as D.

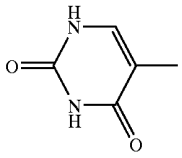
(ii)



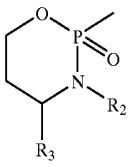
(iii)



(iv)

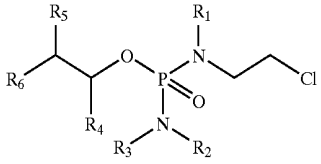


[0250] Examples of suitable nitrogen mustards are disclosed in U.S. Pat. No. 3,808,297, wherein A is:



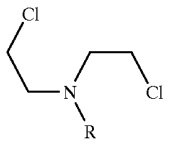
[0251] R_{1-2} are H or CH_2CH_2Cl; R_3 is H or oxygen-containing groups such as hydroperoxy; and R_4 can be alkyl, aryl, heterocyclic.

[0252] The cyclic moiety need not be intact. See, e.g., U.S. Pat. Nos. 5,472,956, 4,908,356, 4,841,085 that describe the following type of structure:

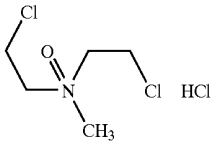


[0253] wherein R_1 is H or CH_2CH_2Cl, and R_{26} are various substituent groups.

[0254] Exemplary nitrogen mustards include methylchloroethamine, and analogues or derivatives thereof, including methylchloroethamine oxide hydrohchloride, novembichin, and mannomustine (a halogenated sugar). Exemplary compounds have the structures:

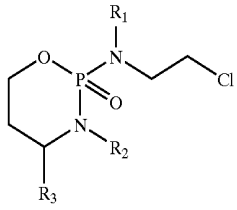


R	
Mechlorethanime	CH_3
Novembichin	$CH_2CH(CH_3)Cl$



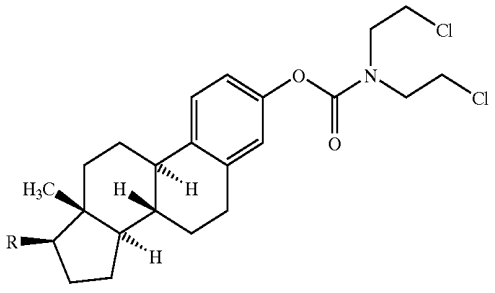
Mechlorethanime Oxide HCl

[0255] The nitrogen mustard may be cyclophosphamide, ifosfamide, perfosfamide, or torofosfamide, where these compounds have the structures:



	R_1	R_2	R_3
Cyclophosphamide	H	CH_2CH_2Cl	H
Ifosfamide	CH_2CH_2CXl	H	H
Perfosfamide	CH_2CH_2Cl	H	OOH
Torofosfamide	CH_2CH_2Cl	CH_2CH_2Cl	H

[0256] The nitrogen mustard may be estramustine, or an analogue or derivative thereof, including phenesterine, prednimustine, and estramustine PO_4. Thus, suitable nitrogen mustard type cell cycle inhibitors of the present invention have the structures:



R	
Estramustine	OH
Phenesterine	$C(CH_3)(CH_2)_3CH(CH_3)_2$

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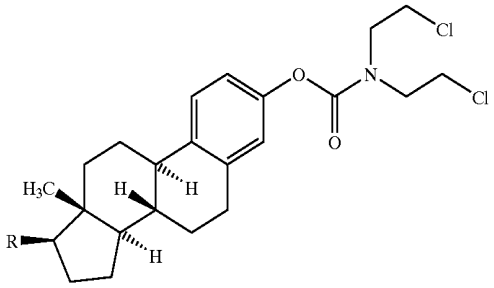
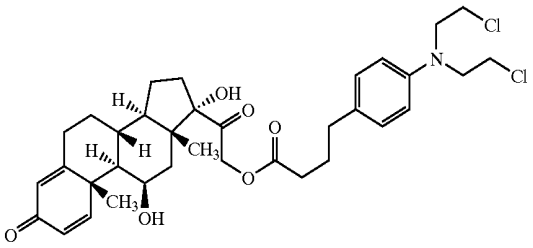
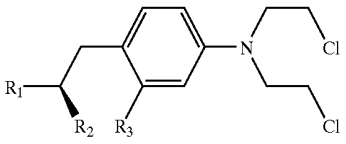


R



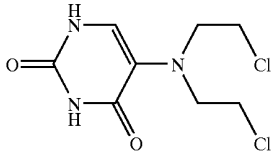
Prednimustine

[0257] The nitrogen mustard may be chlorambucil, or an analogue or derivative thereof, including melphalan and chlormaphazine. Thus, suitable nitrogen mustard type cell cycle inhibitors of the present invention have the structures:



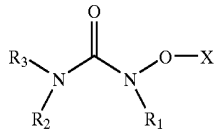
	R_1	R_2	R_3
Chlorambucil	CH_2COOH	H	H
Melphalan	COOH	NH_2	H
Chlornaphazine	H	together forms a benzene ring	

[0258] The nitrogen mustard may be uracil mustard, which has the structure:

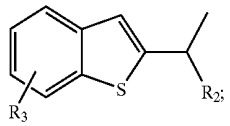


[0259] The nitrogen mustards are thought to function as cell cycle inhibitors by serving as alkylating agents for DNA. Nitrogen mustards have been shown useful in the treatment of cell proliferative disorders including, for example, small cell lung, breast, cervical, head and neck, prostate, retinoblastoma, and soft tissue sarcoma.

[0260] The cell cycle inhibitor of the present invention may be a hydroxyurea. Hydroxyureas have the following general structure:



[0261] Suitable hydroxyureas are disclosed in, for example, U.S. Pat. No. 6,080,874, wherein R_1 is:

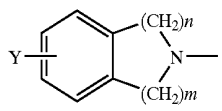


[0262] and R_2 is an alkyl group having 1-4 carbons and R_3 is one of H, acyl, methyl, ethyl, and mixtures thereof, such as a methylether.

[0263] Other suitable hydroxyureas are disclosed in, e.g., U.S. Pat. No. 5,665,768, wherein R_1 is a cycloalkenyl group, for example N-(3-(5-(4-fluorophenylthio)-furyl)-2-cyclopenten-1-yl)N-hydroxyurea; R_2 is H or an alkyl group having 1 to 4 carbons and R_3 is H; X is H or a cation.

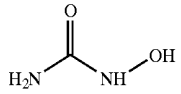
[0264] Other suitable hydroxyureas are disclosed in, e.g., U.S. Pat. No. 4,299,778, wherein R_1 is a phenyl group substituted with on or more fluorine atoms; R_2 is a cyclopropyl group; and R_3 and X is H.

[0265] Other suitable hydroxyureas are disclosed in, e.g., U.S. Pat. No. 5,066,658, wherein R_2 and R_3 together with the adjacent nitrogen form:



[0266] wherein m is 1 or 2, n is 0-2 and Y is an alkyl group.

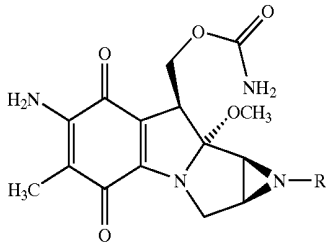
[0267] In one aspect, the hydroxy urea has the structure:



Hydroxyurea

[0268] Hydroxyureas are thought to function as cell cycle inhibitors by serving to inhibit DNA synthesis.

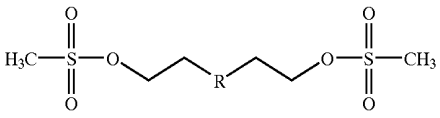
[0269] In another aspect, the cell cycle inhibitor is a mytomicin, such as mitomycin C, or an analogue or derivative thereof, such as porphyromycin. Exemplary compounds have the structures:

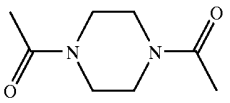
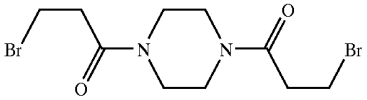


	R
Mitomycin C	H
Porphyromycin (N-methyl Mitomycin C)	CH_3

[0270] These compounds are thought to function as cell cycle inhibitors by serving as DNA alkylating agents. Mitomycins have been shown useful in the treatment of cell proliferative disorders such as, for example, esophageal, liver, bladder, and breast cancers.

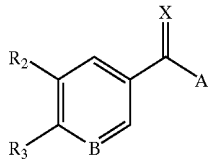
[0271] In another aspect, the cell cycle inhibitor is an alkyl sulfonate, such as busulfan, or an analogue or derivative thereof, such as treosulfan, improsulfan, piposulfan, and pipobroman. Exemplary compounds have the structures:



	R
Busulfan	single bond
Improsulfan	—CH_2—NH—CH_2—
Piposulfan	
	
	Pipobroman

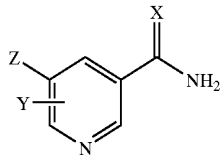
[0272] These compounds are thought to function as cell cycle inhibitors by serving as DNA alkylating agents.

[0273] In another aspect, the cell cycle inhibitor is a benzamide. In yet another aspect, the cell cycle inhibitor is a nicotinamide. These compounds have the basic structure:



[0274] wherein X is either O or S; A is commonly NH_2 or it can be OH or an alkoxy group; B is N or C—R_4, where R_4 is H or an ether-linked hydroxylated alkane such as OCH_2CH_2OH, the alkane may be linear or branched and may contain one or more hydroxyl groups. Alternately, B may be N—R_5 in which case the double bond in the ring involving B is a single bond. R_5 may be H, and alkyl or an aryl group (see, e.g., U.S. Pat. No. 4,258,052); R_2 is H, OR_6, SR_6 or NHR_6, where R_6 is an alkyl group; and R_3 is H, a lower alkyl, an ether linked lower alkyl such as —O-Me or —O-ethyl (see, e.g., U.S. Pat. No. 5,215,738).

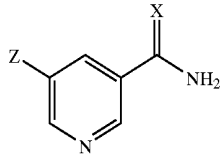
[0275] Suitable benzamide compounds have the structures:



Benzamides
X = O or S
Y = H, OR, CH_3, or acetoxy
Z = H, OR, SR, or NHR
R = alkyl group

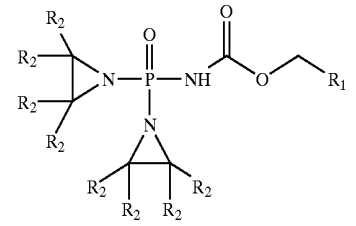
[0276] where additional compounds are disclosed in U.S. Pat. No. 5,215,738, (listing some 32 compounds).

[0277] Suitable nicotinamide compounds have the structures:

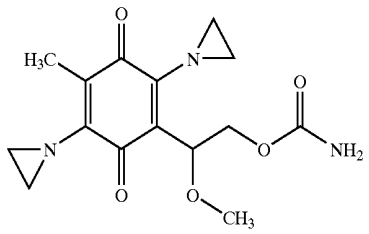


Nicotinamides
X = O or S
Z = H, OR, SR, or NHR
R = alkyl group

[0278] where additional compounds are disclosed in U.S. Pat. No. 5,215,738,

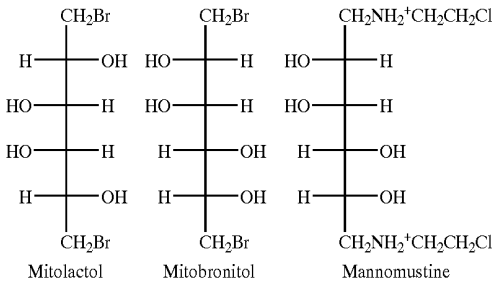


	R_1	R_2
Benzodepa	phenyl	H
Meturedepa	CH_3	CH_3
Uredepa	CH_3	H



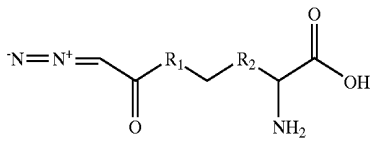
Carboquone

[0279] In another aspect, the cell cycle inhibitor is a halogenated sugar, such as mitolactol, or an analogue or derivative thereof, including mitobronitol and mannomustine. Exemplary compounds have the structures:



Mitolactol Mitobronitol Mannomustine

[0280] In another aspect, the cell cycle inhibitor is a diazo compound, such as azaserine, or an analogue or derivative thereof, including 6-diazo-5-oxo-L-norleucine and 5-diazouracil (also a pyrimidine analog). Exemplary compounds have the structures:



	R_1	R_2
Azaserine	O	single bond
6-diazo-5-oxo-L-norleucine	single bond	CH_2

[0281] Other compounds that may serve as cell cycle inhibitors according to the present invention are pazelliptine; wortmannin; metoclopramide; RSU; buthionine sulfoxime; tumeric; curcumin; AG337, a thymidylate synthase inhibitor; levamisole; lentinan, a polysaccharide; razoxane, an EDTA analogue; indomethacin; chlorpromazine; α and β interferon; MnBOPP; gadolinium texaphyrin; 4-amino-1,8-naphthalimide; staurosporine derivative of CGP; and SR-2508.

[0282] Thus, in one aspect, the cell cycle inhibitor is a DNA alylating agent. In another aspect, the cell cycle inhibitor is an anti-microtubule agent. In another aspect, the cell cycle inhibitor is a topoisomerase inhibitor. In another aspect, the cell cycle inhibitor is a DNA cleaving agent. In another aspect, the cell cycle inhibitor is an antimetabolite. In another aspect, the cell cycle inhibitor functions by inhibiting adenosine deaminase (e.g., as a purine analogue). In another aspect, the cell cycle inhibitor functions by inhibiting purine ring synthesis and/or as a nucleotide interconversion inhibitor (e.g., as a purine analogue such as mercaptopurine). In another aspect, the cell cycle inhibitor functions by inhibiting dihydrofolate reduction and/or as a thymidine monophosphate block (e.g., methotrexate). In another aspect, the cell cycle inhibitor functions by causing DNA damage (e.g., bleomycin). In another aspect, the cell cycle inhibitor functions as a DNA intercalation agent and/or RNA synthesis inhibition (e.g., doxorubicin, aclarubicin, or detorubicin (acetic acid, diethoxy-, 2-[4-[(3-amino-2,3,6-trideoxy-alpha-L-lyxo-hexopyranosyl)oxy]-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-2-naphthacenyl]-2-oxoethyl ester, (2S-cis)-)). In another aspect, the cell cycle inhibitor functions by inhibiting pyrimidine synthesis (e.g., N-phosphonoacetyl-L-aspartate). In another aspect, the cell cycle inhibitor functions by inhibiting ribonucleotides (e.g., hydroxyurea). In another aspect, the cell cycle inhibitor functions by inhibiting thymidine monophosphate (e.g., 5-fluorouracil). In another aspect, the cell cycle inhibitor functions by inhibiting DNA synthesis (e.g., cytarabine). In another aspect, the cell cycle inhibitor functions by causing DNA adduct formation (e.g., platinum compounds). In another aspect, the cell cycle inhibitor functions by inhibiting protein synthesis (e.g., L-asparginase). In another aspect, the cell cycle inhibitor functions by inhibiting microtubule function (e.g., taxanes). In another

aspect, the cell cycle inhibitor acts at one or more of the steps in the biological pathway shown in **FIG. 1**.

[**0283**] Additional cell cycle inhibitor s useful in the present invention, as well as a discussion of the mechanisms of action, may be found in Hardman J. G., Limbird L. E. Molinoff R. B., Ruddon R W., Gilman A. G. editors, Chemotherapy of Neoplastic Diseases in Goodman and Gilman's The Pharmacological Basis of Therapeutics Ninth Edition, McGraw-Hill Health Professions Division, New York, 1996, pages 1225-1287. See also U.S. Pat. Nos. 3,387,001; 3,808,297; 3,894,000; 3,991,045; 4,012,390; 4,057,548; 4,086,417; 4,144,237; 4,150,146; 4,210,584; 4,215,062; 4,250,189; 4,258,052; 4,259,242; 4,296,105; 4,299,778; 4,367,239; 4,374,414; 4,375,432; 4,472,379; 4,588,831; 4,639,456; 4,767,855; 4,828,831; 4,841,045; 4,841,085; 4,908,356; 4,923,876; 5,030,620; 5,034,320; 5,047,528; 5,066,658; 5,166,149; 5,190,929; 5,215,738; 5,292,731; 5,380,897; 5,382,582; 5,409,915; 5,440,056; 5,446,139; 5,472,956; 5,527,905; 5,552,156; 5,594,158; 5,602,140; 5,665,768; 5,843,903; 6,080,874; 6,096,923; and RE030561.

[**0284**] In another embodiment, the cell-cycle inhibitor is camptothecin, mitoxantrone, etoposide, 5-fluorouracil, doxorubicin, methotrexate, peloruside A, mitomycin C, or a CDK-2 inhibitor or an analogue or derivative of any member of the class of listed compounds.

[**0285**] In another embodiment, the cell-cycle inhibitor is HTI-286, plicamycin; or mithramycin, or an analogue or derivative thereof.

[**0286**] Other examples of cell cycle inhibitors also include, e.g., 7-hexanoyltaxol (QP-2), cytochalasin A, lantrunculin D, actinomycin-D, Ro-31-7453 (3-(6-nitro-1-methyl-3-indolyl)-4-(1-methyl-3-indolyl)pyrrole-2,5-dione), PNU-151807, brostallicin, C2-ceramide, cytarabine ocfosfate (2(1H)-pyrimidinone, 4-amino-1-(5-O-(hydroxy(octadecyloxy)phosphinyl)-β-D-arabinofuranosyl)-, monosodium salt), paclitaxel (5β,20-epoxy-1,2 alpha,4,7β,10β,13 alpha-hexahydroxytax-11-en-9-one-4,10-diacetate-2-benzoate-13-(alpha-phenylhippurate)), doxorubicin (5,12-naphthacenedione, 10-((3-amino-2,3,6-trideoxy-alpha-L-lyxo-hexopyranosyl)oxy)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S)-cis-), daunorubicin (5,12-naphthacenedione, 8-acetyl-10-((3-amino-2,3,6-trideoxy-alpha-L-lyxo-hexopyranosyl)oxy)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S-cis)-), gemcitabine hydrochloride (cytidine, 2'-deoxy-2',2'-difluoro-, monohydrochloride), nitacrine (1,3-propanediamine, N,N-dimethyl-N'-(1-nitro-9-acridinyl)-), carboplatin (platinum, diammine(1,1-cyclobutanedicarboxylato(2-)-, (SP-4-2)-), altretamine (1,3,5-triazine-2,4,6-triamine, N,N,N',N',N",N"-hexamethyl-), teniposide (furo(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6(5aH)-one, 5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-9-((4,6-O-(2-thienylmethylene)-β-D-glucopyranosyl)oxy)-, (5R-(5alpha,5aβ,8aAlpha,9β(R*)))-), eptaplatin (platinum, ((4R,5R)-2-(1-methylethyl)-1,3-dioxolane-4,5-dimethanamine-kappa N4,kappa N5)(propanedioato(2-)-kappa O1, kappa O3)-, (SP-4-2)-), amrubicin hydrochloride (5,12-naphthacenedione, 9-acetyl-9-amino-7-((2-deoxy-β-D-erythro-pentopyranosyl)oxy)-7,8,9,10-tetrahydro-6,11-dihydroxy-, hydrochloride, (7S-cis)-), ifosfamide (2H-1,3,2-oxazaphosphorin-2-amine, N,3-bis(2-chloroethyl)tetrahydro-,2-oxide), cladribine (adenosine, 2-chloro-2'-deoxy-), mitobronitol (D-mannitol, 1,6-dibromo-1,6-dideoxy-), fludaribine phosphate (9H-purin-6-amine, 2-fluoro-9-(5-O-phosphono-β-D-arabinofuranosyl)-), enocitabine (docosanamide, N-(1-β-D-arabinofuranosyl-1,2-dihydro-2-oxo-4-pyrimidinyl)-), vindesine (vincaleukoblastine, 3-(aminocarbonyl)-O4-deacetyl-3-de(methoxycarbonyl)-), idarubicin (5,12-naphthacenedione, 9-acetyl-7-((3-amino-2,3,6-trideoxy-alpha-L-lyxo-hexopyranosyl)oxy)-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S-cis)-), zinostatin (neocarzinostatin), vincristine (vincaleukoblastine, 22-oxo-), tegafur (2,4(1H,3H)-pyrimidinedione, 5-fluoro-1-(tetrahydro-2-furanyl)-), razoxane (2,6-piperazinedione, 4,4'-(1-methyl-1,2-ethanediyl)bis-), methotrexate (L-glutamic acid, N-(4-(((2,4-diamino-6-pteridinyl)methyl-)methylamino)benzoyl)-), raltitrexed (L-glutamic acid, N-((5-(((1,4-dihydro-2-methyl-4-oxo-6-quinazolinyl)methyl)methylamino)-2-thienyl)carbonyl)-), oxaliplatin (platinum, (1,2-cyclohexanediamine-N,N')(ethanedioato(2-)-O, O'), (SP-4-2-(1R-trans))-), doxifluridine (uridine, 5'-deoxy-5-fluoro-), mitolactol (galactitol, 1,6-dibromo-1,6-dideoxy-), piraubicin (5,12-naphthacenedione, 10-((3-amino-2,3,6-trideoxy-4-O-(tetrahydro-2H-pyran-2-yl)-alpha-L-lyxo-hexopyranosyl)oxy)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S-(8 alpha, 10 alpha(S*)))-), docetaxel ((2R,3S)-N-carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5β,20-epoxy-1,2 alpha,4,7β,10β,13 alpha-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate-), capecitabine (cytidine, 5-deoxy-5-fluoro-N-((pentyloxy)carbonyl)-), cytarabine (2(1H)-pyrimidone, 4-amino-1-β-D-arabino furanosyl-), valrubicin (pentanoic acid, 2-(1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-4-((2,3,6-trideoxy-3-((trifluoroacetyl)amino)-alpha-L-lyxo-hexopyranosyl)oxy)-2-naphthacenyl)-2-oxoethyl ester (2S-cis)-), trofosfamide (3-2-(chloroethyl)-2-(bis(2-chloroethyl)amino)tetrahydro-2H-1,3,2-oxazaphosphorin 2-oxide), prednimustine (pregna-1,4-diene-3,20-dione, 21-(4-(4-(bis(2-chloroethyl)amino)phenyl)-1-oxobutoxy)-11,17-dihydroxy-, (11β)-), lomustine (Urea, N-(2-chloroethyl)-N'-cyclohexyl-N-nitroso-), epirubicin (5,12-naphthacenedione, 10-((3-amino-2,3,6-trideoxy-alpha-L-arabino-hexopyranosyl)oxy)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S-cis)-), or an analogue or derivative thereof).

[**0287**] 5) Cyclin Dependent Protein Kinase Inhibitors

[**0288**] In another embodiment, the pharmacologically active compound is a cyclin dependent protein kinase inhibitor (e.g., R-roscovitine, CYC-101, CYC-103, CYC-400, MX-7065, alvocidib (4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methyl-4-piperidinyl)-, cis-(−)-), SU-9516, AG-12275, PD-0166285, CGP-79807, fascaplysin, GW-8510 (benzenesulfonamide, 4-(((Z)-(6,7-dihydro-7-oxo-8H-pyrrolo(2,3-g)benzothiazol-8-ylidene)methyl)amino)-N-(3-hydroxy-2,2-dimethylpropyl)-), GW-491619, Indirubin 3' monoxime, GW8510, AZD-5438, ZK-CDK or an analogue or derivative thereof).

[**0289**] 6) EGF (Epidermal Growth Factor) Receptor Kinase Inhibitors

[**0290**] In another embodiment, the pharmacologically active compound is an EGF (epidermal growth factor) kinase inhibitor (e.g., erlotinib (4-quinazolinamine, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-, monohydro-

chloride), erbstatin, BIBX-1382, gefitinib (4-quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-(4-morpholinyl)propoxy)), or an analogue or derivative thereof).

[0291] 7) Elastase Inhibitors

[0292] In another embodiment, the pharmacologically active compound is an elastase inhibitor (e.g., ONO-6818, sivelestat sodium hydrate (glycine, N-(2-(((4-(2,2-dimethyl-1-oxopropoxy)phenyl)sulfonyl)amino)benzoyl)-), erdosteine (acetic acid, ((2-oxo-2-((tetrahydro-2-oxo-3-thienyl)amino)ethyl)thio)-), MDL-100948A, MDL-104238 (N-(4-(4-morpholinylcarbonyl)benzoyl)-L-valyl-N'-(3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl)-L-2-azetamide), MDL-27324 (L-prolinamide, N-((5-(dimethylamino)-1-naphthalenyl)sulfonyl)-L-alanyl-L-alanyl-N-(3,3,3-trifluoro-1-(1-methylethyl)-2-oxopropyl)-, (S)-), SR-26831 (thieno(3,2-c)pyridinium, 5-((2-chlorophenyl)methyl)-2-(2,2-dimethyl-1-oxopropoxy)-4,5,6,7-tetrahydro-5-hydroxy-), Win-68794, Win-63110, SSR-69071 (2-(9(2-piperidinoethoxy)-4-oxo-4H-pyrido(1,2-a)pyrimidin-2-yloxymethyl)-4-(1-methylethyl)-6-methyoxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxide), (N(Alpha)-(1-adamantylsulfonyl)N(epsilon)-succinyl-L-lysyl-L-prolyl-L-valinal), Ro-31-3537 (N alpha-(1-adamantanesulphonyl)-N-(4-carboxybenzoyl)-L-lysyl-alanyl-L-valinal), R-665, FCE-28204, ((6R,7R)-2-(benzoyloxy)-7-methoxy-3-methyl-4-pivaloyl-3-cephem 1,1-dioxide), 1,2-benzisothiazol-3(2H)-one, 2-(2,4-dinitrophenyl)-, 1,1-dioxide, L-658758 (L-proline, 1-((3-((acetyloxy)methyl)-7-methoxy-8-oxo-5-thia-1-azabicyclo(4.2.0)oct-2-en-2-yl)carbonyl)-, S,S-dioxide, (6R-cis)-), L-659286 (pyrrolidine, 1-((7-methoxy-8-oxo-3-(((1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-yl)thio)methyl)-5-thia-1-azabicyclo(4.2.0)oct-2-en-2-yl)carbonyl)-, S,S-dioxide, (6R-cis)-), L-680833 (benzeneacetic acid, 4-((3,3-diethyl-1-(((1-(4-methylphenyl)butyl)amino)carbonyl)-4-oxo-2-azetidinyl)oxy)-, (S-(R*,S*))-), FK-706 (L-prolinamide, N-[4-[[(carboxymethyl)amino]carbonyl]benzoyl]-L-valyl-N-[3,3,3-trifluoro-1-(1-methylethyl)-2-oxopropyl]-, monosodium salt), Roche R-665, or an analogue or derivative thereof).

[0293] 8) Factor Xa Inhibitors

[0294] In another embodiment, the pharmacologically active compound is a factor Xa inhibitor (e.g., CY-222, fondaparinux sodium (alpha-D-glucopyranoside, methyl O-2-deoxy-6-O-sulfo-2-(sulfoamino)-alpha-D-glucopyranosyl-(1-4)-O-β-D-glucopyranuronosyl-(1-4)-O-2-deoxy-3,6-di-O-sulfo-2-(sulfoamino)-alpha-D-glucopyranosyl-(1-4)-O-2-O-sulfo-alpha-L-idopyranuronosyl-(1-4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate)), danaparoid sodium, or an analogue or derivative thereof).

[0295] 9) Famesyltransferase Inhibitors

[0296] In another embodiment, the pharmacologically active compound is a farnesyltransferase inhibitor (e.g., dichlorobenzoprim (2,4-diamino-5-(4-(3,4-dichlorobenzylamino)-3-nitrophenyl)-6-ethylpyrimidine), B-581, B-956 (N-(8(R)-amino-2(S)-benzyl-5(S)-isopropyl-9-sulfanyl-3(Z),6(E)-nonadienoyl)-L-methionine), OSI-754, perillyl alcohol (1-cyclohexene-1-methanol, 4-(1-methylethenyl)-, RPR-114334, lonafarnib (1-piperidinecarboxamide, 4-(2-(4-((11R)-3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo(5,6)cyclohepta(1,2-b)pyridin-11-yl)-1-piperidinyl)-2-oxoethyl)-), Sch-48755, Sch-226374, (7,8-dichloro-5H-dibenzo(b,e)(1,4)diazepin-11-yl)-pyridin-3-ylmethylamine, J-104126, L-639749, L-731734 (pentanamide, 2-((2-((2-amino-3-mercaptopropyl)amino)-3-methylpentyl)amino)-3-methyl-N-(tetrahydro-2-oxo-3-furanyl)-, (3S-(3R*(2R*(2R*(S*),3S*),3R*)))-), L-744832 (butanoic acid, 2-((2-((2-((2-amino-3-mercaptopropyl)amino)-3-methylpentyl)oxy)-1-oxo-3-phenylpropyl)amino)-4-(methylsulfonyl)-, 1-methylethyl ester, (2S-(1(R*(R*)),2R*(S*),3R*))-), L-745631 (1-piperazinepropanethiol, 1-amino-2-(2-methoxyethyl)-4-(1-naphthalenylcarbonyl)-, (βR,2S)-), N-acetyl-N-naphthylmethyl-2(S)-((1-(4-cyanobenzyl)-1H-imidazol-5-yl)acetyl)amino-3(S)-methylpentamine, (2alpha)-2-hydroxy-24,25-dihydroxylanost-8-en-3-one, BMS-316810, UCF-1-C (2,4-decadienamide, N-(5-hydroxy-5-(7-((2-hydroxy-5-oxo-1-cyclopenten-1-yl)amino-oxo-1,3,5-heptatrienyl)-2-oxo-7-oxabicyclo(4.1.0)hept-3-en-3-yl)-2,4,6-trimethyl-, (1S-(1 alpha,3(2E,4E,6S*),5 alpha, 5(1E,3E,5E), 6 alpha))-), UCF-116-B, ARGLABIN (3H-oxireno[8,8a]azuleno[4,5-b]furan-8(4aH)-one, 5,6,6a,7,9a,9b-hexahydro-1,4a-dimethyl-7-methylene-, (3aR,4aS,6aS,9aS,9bR)-) from ARGLABIN—Paracure, Inc. (Virginia Beach, Va.), or an analogue or derivative thereof).

[0297] 10) Fibrinogen Antagonists

[0298] In another embodiment, the pharmacologically active compound is a fibrinogen antagonist (e.g., 2(S)-((p-toluenesulfonyl)amino)-3-(((5,6,7,8,-tetrahydro-4-oxo-5-(2-(piperidin-4-yl)ethyl)-4H-pyrazolo-(1,5-a)(1,4)diazepin-2-yl)carbonyl]amino)propionic acid, streptokinase (kinase (enzyme-activating), strepto-), urokinase (kinase (enzyme-activating), uro-), plasminogen activator, pamiteplase, monteplase, heberkinase, anistreplase, alteplase, pro-urokinase, picotamide (1,3-benzenedicarboxamide, 4-methoxy-N,N'-bis(3-pyridinylmethyl)-), or an analogue or derivative thereof).

[0299] 11) Guanylate Cyclase Stimulants

[0300] In another embodiment, the pharmacologically active compound is a guanylate cyclase stimulant (e.g., isosorbide-5-mononitrate (D-glucitol, 1,4:3,6-dianhydro-, 5-nitrate), or an analogue or derivative thereof).

[0301] 12) Heat Shock Protein 90 Antagonists

[0302] In another embodiment, the pharmacologically active compound is a heat shock protein 90 antagonist (e.g., geldanamycin; NSC-33050 (17-allylaminogeldanamycin), rifabutin (rifamycin XIV, 1',4-didehydro-1-deoxy-1,4-dihydro-5'-(2-methylpropyl)-1-oxo-), 17AAG, or an analogue or derivative thereof).

[0303] 13) HMGCoA Reductase Inhibitors

[0304] In another embodiment, the pharmacologically active compound is an HMGCoA reductase inhibitor (e.g., BCP-671, BB-476, fluvastatin (6-heptenoic acid, 7-(3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl)-3,5-dihydroxy-, monosodium salt, (R*,S*-(E))—(+/−)—), dalvastatin (2H-pyran-2-one, 6-(2-(2-(2-(4-fluoro-3-methylphenyl)-4,4,6,6-tetramethyl-1-cyclohexen-1-yl)ethenyl)tetrahydro)-4-hydroxy-, (4alpha,6β((E))-(+/−)-), glenvastatin (2H-pyran-2-one, 6-(2-(4-(4-fluorophenyl)-2-(1-methylethyl)-6-phenyl-3-pyridinyl)ethenyl)tetrahydro-4-hydroxy-, (4R-(4alpha,6β(E)))-), S-2468, N-(1-oxododecyl)-4Alpha,10-dimethyl-8-aza-trans-decal-3'-ol, atorvastatin calcium (1H-

Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-β,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-((phenylamino)carbonyl)-, calcium salt (R—(R*,R*))-), CP-83101 (6,8-nonadienoic acid, 3,5-dihydroxy-9,9-diphenyl-, methyl ester, (R*,S*-(E))-(+/−)-), pravastatin (1-naphthaleneheptanoic acid, 1,2,6,7,8,8a-hexahydro-β,delta,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-, monosodium salt, (1S-(1 alpha(1S*,deltaS*),2 alpha,6 alpha,8β(R*),8a alpha))-), U-20685, pitavastatin (6-heptenoic acid, 7-(2-cyclopropyl-4-(4-fluorophenyl)-3-quinolinyl)-3,5-dihydroxy-, calcium salt (2:1), (S-(R*,S*-(E)))-), N-((1-methylpropyl)carbonyl)-8-(2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl)-perhydro-isoquinoline, dihydromevinolin (butanoic acid, 2-methyl-, 1,2,3,4,4a,7,8,8a-octahydro-3,7-dimethyl-8-(2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl)-1-naphthalenyl ester(1 alpha(R*), 3 alpha, 4a alpha,7β,8β(2S*,4S*),8aβ))-), HBS-107, dihydromevinolin (butanoic acid, 2-methyl-, 1,2,3,4,4a,7,8,8a-octahydro-3,7-dimethyl-8-(2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl)-1-naphthalenyl ester(1 alpha(R*), 3 alpha,4a alpha,7β,8β(2S*,4S*),8aβ))-), L-669262 (butanoic acid, 2,2-dimethyl-, 1,2,6,7,8,8a-hexahydro-3,7-dimethyl-6-oxo-8-(2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl-)ethyl)-1-naphthalenyl(1S-(1 Alpha,7β,8β(2S*,4S*),8β))-), simvastatin (butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-(2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl)-1-naphthalenyl ester, (1S-(1alpha, 3alpha,7β,8β(2S*,4S*),8β))-), rosuvastatin calcium (6-heptenoic acid, 7-(4-(4-fluorophenyl)-6-(1-methylethyl)-2-(methyl(methylsulfonyl)amino)-5-pyrimdinyl)-3,5-dihydroxy-calcium salt (2:1) (S-(R*,S*-(E)))), meglutol (2-hydroxy-2-methyl-1,3-propandicarboxylic acid), lovastatin (butanoic acid, 2-methyl-, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-(2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl)-1-naphthalenyl ester, (1S-(1 alpha.(R*),3 alpha,7β,8β(2S*,4S*), 8aβ))-), or an analogue or derivative thereof).

[0305] 14) Hydroorotate Dehydrogenase Inhibitors

[0306] In another embodiment, the pharmacologically active compound is a hydroorotate dehydrogenase inhibitor (e.g., leflunomide (4-isoxazolecarboxamide, 5-methyl-N-(4-(trifluoromethyl)phenyl)-), laflunimus (2-propenamide, 2-cyano-3-cyclopropyl-3-hydroxy-N-(3-methyl-4(trifluoromethyl)phenyl)-, (Z)-), or atovaquone (1,4-naphthalenedione, 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-, trans-, or an analogue or derivative thereof).

[0307] 15) IKK2 Inhibitors

[0308] In another embodiment, the pharmacologically active compound is an IKK2 inhibitor (e.g., MLN-120B, SPC-839, or an analogue or derivative thereof).

[0309] 16) IL-1. ICE and IRAK Antagonists

[0310] In another embodiment, the pharmacologically active compound is an IL-1, ICE or an IRAK antagonist (e.g., E-5090 (2-propenoic acid, 3-(5-ethyl-4-hydroxy-3-methoxy-1-naphthalenyl)-2-methyl-, (Z)-), CH-164, CH-172, CH-490, AMG-719, iguratimod (N-(3-(formylamino)-4-oxo-6-phenoxy-4H-chromen-7-yl) methanesulfonamide), AV94-88, pralnacasan (6H-pyridazino(1,2-a)(1,2)diazepine-1-carboxamide, N-((2R,3S)-2-ethoxytetrahydro-5-oxo-3-furanyl)octahydro-9-((1-isoquinolinylcarbonyl)amino)-6,10-dioxo-, (1S,9S)-), (2S-cis)-5-(benzyloxycarbonylamino-1,2,4,5,6,7-hexahydro-4-(oxoazepino(3,2,1-hi)indole-2-carbonyl)-amino)-4-oxobutanoic acid, AVE-9488, esonarimod (benzenebutanoic acid, alpha-((acetylthio)methyl-4-methyl-gamma-oxo-), pralnacasan (6H-pyridazino(1,2-a)(1,2)diazepine-1-carboxamide, N-((2R,3S)-2-ethoxytetrahydro-5-oxo-3-furanyl)octahydro-9-((1-isoquinolinylcarbonyl)amino)-6,10-dioxo-, (1S,9S)-), tranexamic acid (cyclohexanecarboxylic acid, 4-(aminomethyl)-, trans-), Win-72052, romazarit (Ro-31-3948) (propanoic acid, 2-((2-(4-chlorophenyl)-4-methyl-5-oxazolyl)methoxy)-2-methyl-), PD-163594, SDZ-224-015 (L-alaninamide N-((phenylmethoxy)carbonyl)-L-valyl-N-((1S)-3-((2,6-dichlorobenzoyl)oxy)-1-(2-ethoxy-2-oxoethyl)-2-oxopropyl)-), L-709049 (L-alaninamide, N-acetyl-L-tyrosyl-L-valyl-N-(2-carboxy-1-formylethyl)-, (S)-), TA-383 (1H-imidazole, 2-(4-chlorophenyl)-4,5-dihydro-4,5-diphenyl-, monohydrochloride, cis-), EI-1507-1 (6a, 12a-epoxybenz(a)anthracen-1,12(2H,7H)-dione, 3,4-dihydro-3,7-dihydroxy-8-methoxy-3-methyl-), ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-yl methyl)quinoline-3-carboxylate, EI-1941-1, TJ-114, anakinra (interleukin 1 receptor antagonist (human isoform x reduced), N2-L-methionyl-), IX-207-887 (acetic acid, (10-methoxy-4H-benzo[4,5]cyclohepta[1,2-b]thien-4-ylidene)-), K-832, or an analogue or derivative thereof).

[0311] 17) IL-4 Agonists

[0312] In another embodiment, the pharmacologically active compound is an IL-4 agonist (e.g., glatiramir acetate (L-glutamic acid, polymer with L-alanine, L-lysine and L-tyrosine, acetate (salt)), or an analogue or derivative thereof).

[0313] 18) Immunomodulatory Agents

[0314] In another embodiment, the pharmacologically active compound is an immunomodulatory agent (e.g., biolimus, ABT-578, methylsulfamic acid 3-(2-methoxyphenoxy)-2-(((methylamino)sulfonyl)oxy)propyl ester, sirolimus (also referred to as rapamycin or RAPAMUNE (American Home Products, Inc., Madison, N.J.)), CCl-779 (rapamycin 42-(3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate)), LF-15-0195, NPC15669 (L-leucine, N-(((2,7-dimethyl-9H-fluoren-9-yl)methoxy)carbonyl)-), NPC-15670 (L-leucine, N-(((4,5-dimethyl-9H-fluoren-9-yl-)methoxy)carbonyl)-), NPC-16570 (4-(2-(fluoren-9-yl)ethyloxy-carbonyl)aminobenzoic acid), sufosfamide (ethanol, 2-((3-(2-chloroethyl)tetrahydro-2H-1,3,2-oxazaphosphorin-2-yl)amino)-, methanesulfonate (ester), P-oxide), tresperimus (2-(N-(4-(3-aminopropylamino)butyl)carbamoyloxy)-N-(6-guanidinohexyl)acetamide), 4-(2-(fluoren-9-yl)ethoxycarbonylamino)-benzo-hydroxamic acid, iaquinimod, PBI-1411, azathioprine (6-((1-Methyl-4-nitro-1H-imidazol-5-yl)thio)-1H-purine), PBI0032, beclometasone, MDL-28842 (9H-purin-6-amine, 9-(5-deoxy-5-fluoro-β-D-threo-pent-4-enofuranosyl)-, (Z)-), FK-788, AVE-1726, ZK-90695, ZK-90695, Ro-54864, didemnin-B, Illinois (didemnin A, N-(1-(2-hydroxy-1-oxopropyl)-L-prolyl)-, (S)-), SDZ-62-826 (ethanaminium, 2-((hydroxy((1-((octadecyloxy)carbonyl)-3-piperidinyl)methoxy)phosphinyl)oxy)-N,N,N-trimethyl-, inner salt), argyrin B ((4S,7S,13R, 22R)-13-Ethyl-4-(1H-indol-3-ylmethyl)-7-(4-methoxy-1H-indol-3-ylmethyl)18,22-dimethyl-16-methyl-ene-24-thia-3, 6,9,12,15,18,21,26-octaazabicyclo(21.2.1)-hexacosa-1(25), 23(26)-diene-2,5,8,11,14,17,20-heptaone), everolimus (rapamycin, 42-O-(2-hydroxyethyl)-), SAR-943, L-687795,

6-((4-chlorophenyl)sulfinyl)-2,3-dihydro-2-(4-methoxyphenyl)-5-methyl-3-oxo-4-pyridazinecarbonitrile, 91Y78 (1H-imidazo[4,5-c)pyridin-4-amine, 1-β-D-ribofuranosyl-), auranofin (gold, (1-thio-β-D-glucopyranose 2,3,4,6-tetraacetato-S)(triethylphosphine)-), 27-0-demethylrapamycin, tipredane (androsta-1,4-dien-3-one, 17-(ethylthio)-9-fluoro-11-hydroxy-17-(methylthio)-, (11β,17 alpha)-), AI-402, LY-178002 (4-thiazolidinone, 5-((3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl)methylene)-), SM-8849 (2-thiazolamine, 4-(1-(2-fluoro(1,1'-biphenyl)-4-yl)ethyl)-N-methyl-), piceatannol, resveratrol, triamcinolone acetonide (pregna-1,4-diene-3,20-dione, 9-fluoro-11,21-dihydroxy-16,17-((1-methylethylidene)bis(oxy))-, (11β,16 alpha)-), ciclosporin (cyclosporin A), tacrolimus (15,19-epoxy-3H-pyrido(2,1-c)(1,4)oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-(2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl)-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-, (3S-(3R*(E(1S*,3S*,4S*)),4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*))-), gusperimus (heptanamide, 7-((aminoiminomethyl)amino)-N-(2-((4-((3-aminopropyl)amino)butyl)amino)-1-hydroxy-2-oxoethyl)-, (+/−)-), tixocortol pivalate (pregn-4-ene-3,20-dione, 21-((2,2-dimethyl-1-oxopropyl)thio)-11,17-dihydroxy-, (11β)-), alefacept (1-92 LFA-3 (antigen) (human) fusion protein with immunoglobulin G1 (human hinge-CH2-CH3 gamma1-chain), dimer), halobetasol propionate (pregna-1,4-diene-3,20-dione, 21-chloro-6,9-difluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)-, (6Alpha,11β,16β), iloprost trometamol (pentanoic acid, 5-(hexahydro-5-hydroxy-4-(3-hydroxy-4-methyl-1-octen-6-ynyl)-2(1H)-pentalenylidene)-), beraprost (1H-cyclopenta(b)benzofuran-5-butanoic acid, 2,3,3a,8b-tetrahydro-2-hydroxy-1-(3-hydroxy-4-methyl-1-octen-6-ynyl)-), rimexolone (androsta-1,4-dien-3-one, 11-hydroxy-16,17-dimethyl-17-(1-oxopropyl)-, (11β,16Alpha, 17β)-), dexamethasone (pregna-1,4-diene-3,20-dione,9-fluoro-11,17,21-trihydroxy-16-methyl-, (11β,16alpha)-), sulindac (cis-5-fluoro-2-methyl-1-((p-methylsulfinyl)benzylidene)indene-3-acetic acid), proglumetacin (1H-Indole-3-acetic acid, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-, 2-(4-(3-((4-(benzoylamino)-5-(dipropylamino)-1,5-dioxopentyl)oxy)propyl)-1-piperazinyl)ethylester, (+/−)-), alclometasone dipropionate (pregna-1,4-diene-3,20-dione, 7-chloro-11-hydroxy-16-methyl-17,21-bis(1-oxopropoxy)-, (7alpha,11β,16alpha)-), pimecrolimus (15,19-epoxy-3H-pyrido(2,1-c)(1,4)oxaazacyclotricosine-1,7,20,21 (4H,23H)-tetrone, 3-(2-(4-chloro-3-methoxycyclohexyl)-1-methyletheny)-8-ethyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-, (3S-(3R*(E(1S*,3S*,4R*)),4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*))-), hydrocortisone-17-butyrate (pregn-4-ene-3,20-dione, 11,21-dihydroxy-17-(1-oxobutoxy)-, (11β)-), mitoxantrone (9,10-anthracenedione, 1,4-dihydroxy-5,8-bis((2-((2-hydroxyethyl)amino)ethyl)amino)-), mizoribine (1H-imidazole-4-carboxamide, 5-hydroxy-1-β-D-ribofuranosyl-), prednicarbate (pregna-1,4-diene-3,20-dione, 17-((ethoxycarbonyl)oxy)-11-hydroxy-21-(1-oxopropoxy)-, (11β)-), iobenzarit (benzoic acid, 2-((2-carboxyphenyl)amino)-4-chloro-), glucametacin (D-glucose, 2-(((1-(4-chlorobenzoyl)-5-methoxy-2-methyl-11H-indol-3-yl)acetyl)amino)-2-deoxy-), fluocortolone monohydrate ((6 alpha)-fluoro-16alpha-methylpregna-1,4-dien-11β,21-diol-3,20-dione), fluocortin butyl (pregna-1,4-dien-21-oic acid, 6-fluoro-11-hydroxy-16-methyl-3,20-dioxo-, butyl ester, (6alpha,11β,16alpha)-), difluprednate (pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-6,9-difluoro-11-hydroxy-17-(1-oxobutoxy)-, (6 alpha,11β)-), diflorasone diacetate (pregna-1,4-diene-3,20-dione, 17,21-bis(acetyloxy)-6,9-difluoro-11-hydroxy-16-methyl-, (6Alpha,11β,16β)-), dexamethasone valerate (pregna-1,4-diene-3,20-dione, 9-fluoro-11,21-dihydroxy-16-methyl-17-((1-oxopentyl)oxy)-, (11β,16Alpha)-), methylprednisolone, deprodone propionate (pregna-1,4-diene-3,20-dione, 11-hydroxy-17-(1-oxopropoxy)-, (11.beta.)-), bucillamine (L-cysteine, N-(2-mercapto-2-methyl-1-oxopropyl)-), amcinonide (benzeneacetic acid, 2-amino-3-benzoyl-, monosodium salt, monohydrate), acemetacin (1H-indole-3-acetic acid, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-, carboxymethyl ester), or an analogue or derivative thereof).

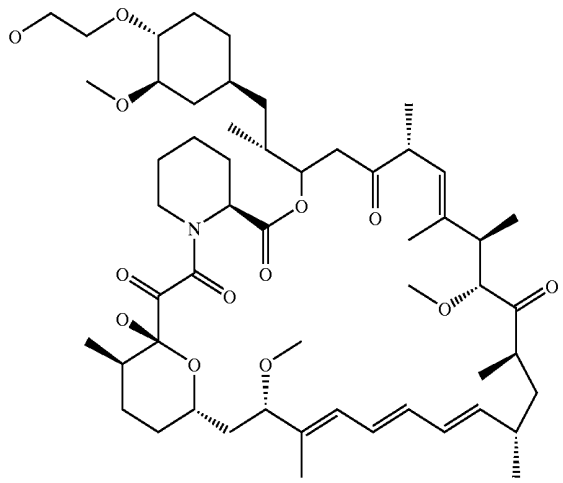
[**0315**] Further, analogues of rapamycin include tacrolimus and derivatives thereof (e.g., EP0184162B1 and U.S. Pat. No. 6,258,823) everolimus and derivatives thereof (e.g., U.S. Pat. No. 5,665,772). Further representative examples of sirolimus analogues and derivatives can be found in PCT Publication Nos. WO 97/10502, WO 96/41807, WO 96/35423, WO 96/03430, WO 96/00282, WO 95/16691, WO 95/15328, WO 95/07468, WO 95/04738, WO 95/04060, WO 94/25022, WO 94/21644, WO 94/18207, WO 94/10843, WO 94/09010, WO 94/04540, WO 94/02485, WO 94/02137, WO 94/02136, WO 93/25533, WO 93/18043, WO 93/13663, WO 93/11130, WO 93/10122, WO 93/04680, WO 92/14737, and WO 92/05179. Representative U.S. patents include U.S. Pat. Nos. 6,342,507; 5,985,890; 5,604,234; 5,597,715; 5,583,139; 5,563,172; 5,561,228; 5,561,137; 5,541,193; 5,541,189; 5,534,632; 5,527,907; 5,484,799; 5,457,194; 5,457,182; 5,362,735; 5,324,644; 5,318,895; 5,310,903; 5,310,901; 5,258,389; 5,252,732; 5,247,076; 5,225,403; 5,221,625; 5,210,030; 5,208,241; 5,200,411; 5,198,421; 5,147,877; 5,140,018; 5,116,756; 5,109,112; 5,093,338; and 5,091,389.

[**0316**] The structures of sirolimus, everolimus, and tacrolimus are provided below:

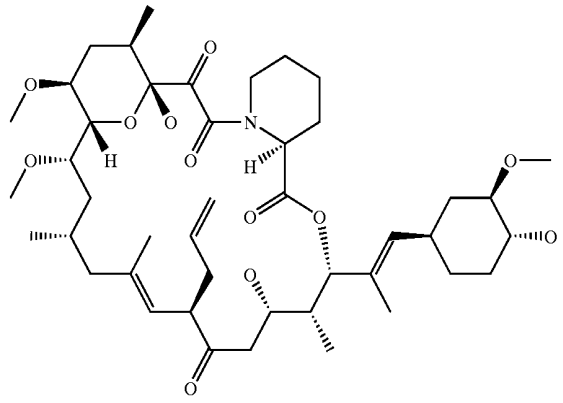
Name	Code Name	Company	Structure
Everolimus	SAR-943	Novartis	See below
Sirolimus	AY-22989	Wyeth	See below

-continued

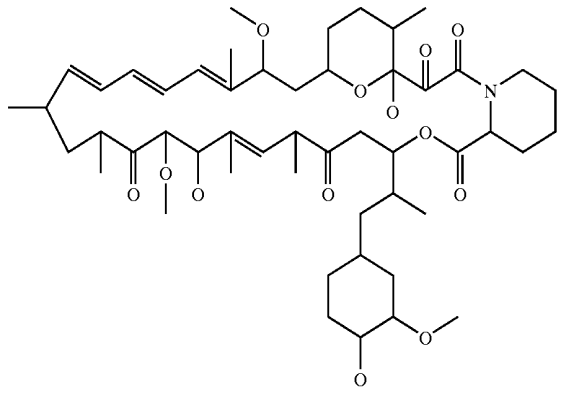
Name	Code Name	Company	Structure
RAPAMUNE	NSC-226080		
Rapamycin			
Tacrolimus	FK506	Fujusawa	See below



Everolimus



Tacrolimus



Sirolimus

[0317] Further sirolimus analogues and derivatives include tacrolimus and derivatives thereof (e.g., EP0184162B1 and U.S. Pat. No. 6,258,823) everolimus and derivatives thereof (e.g., U.S. Pat. No. 5,665,772). Further representative examples of sirolimus analogues and derivatives include ABT-578 and others may be found in PCT Publication Nos. WO 97/10502, WO 96/41807, WO 96/35423, WO 96/03430, WO 9600282, WO 95/16691, WO 9515328, WO 95/07468, WO 95/04738, WO 95/04060, WO 94/25022, WO 94/21644, WO 94/18207, WO 94/10843, WO 94/09010, WO 94/04540, WO 94/02485, WO 94/02137, WO 94/02136, WO 93/25533, WO 93/18043, WO 93/13663, WO 93/11130, WO 93/10122, WO 93/04680, WO 92/14737, and WO 92/05179. Representative U.S. patents include U.S. Pat. Nos. 6,342,507; 5,985,890; 5,604,234; 5,597,715; 5,583,139; 5,563,172; 5,561,228; 5,561,137; 5,541,193; 5,541,189; 5,534,632; 5,527,907; 5,484,799; 5,457,194; 5,457,182; 5,362,735; 5,324,644; 5,318,895; 5,310,903; 5,310,901; 5,258,389; 5,252,732; 5,247,076; 5,225,403; 5,221,625; 5,210,030; 5,208,241, 5,200,411; 5,198,421; 5,147,877; 5,140,018; 5,116,756; 5,109,112; 5,093,338; and 5,091,389.

[0318] In one aspect, the fibrosis-inhibiting agent may be, e.g., rapamycin (sirolimus), everolimus, biolimus, tresperimus, auranofin, 27-0-demethylrapamycin, tacrolimus, gusperimus, pimecrolimus, or ABT-578.

[0319] 19) Inosine Monophosphate Dehydrogenase Inhibitors

[0320] In another embodiment, the pharmacologically active compound is an inosine monophosphate dehydrogenase (IMPDH) inhibitor (e.g., mycophenolic acid, mycophenolate mofetil (4-hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (E)-), ribavirin (1H-1,2,4-triazole-3-carboxamide, 1-β-D-ribofuranosyl-), tiazofurin (4-thiazolecarboxamide, 2-β-D-ribofuranosyl-), viramidine, aminothiadiazole, thiophenfurin, tiazofurin) or an analogue or derivative thereof. Additional representative examples are included in U.S. Pat. Nos. 5,536,747, 5,807,876, 5,932,600, 6,054,472, 6,128,582, 6,344,465, 6,395,763, 6,399,773, 6,420,403, 6,479,628, 6,498,178, 6,514,979, 6,518,291, 6,541,496, 6,596,747, 6,617,323, 6,624,184, Patent Application Publication Nos. 2002/0040022A1, 2002/0052513A1, 2002/0055483A1, 2002/0068346A1, 2002/0111378A1, 2002/0111495A1, 2002/0123520A1, 2002/0143176A1, 2002/0147160A1, 2002/0161038A1, 2002/0173491A1, 2002/0183315A1, 2002/0193612A1, 2003/0027845A1, 2003/0068302A1, 2003/0105073A1, 2003/0130254A1, 2003/0143197A1, 2003/0144300A1, 2003/0166201 A1, 2003/0181497A1, 2003/0186974A1, 2003/0186989A1, 2003/0195202A1, and PCT Publication Nos. WO 0024725A1, WO 00/25780A1, WO 00/26197A1, WO 00/51615A1, WO 00/56331A1, WO 00/73288A1, WO 01/00622A1, WO 01/66706A1, WO 01/79246A2, WO 01/81340A2, WO 01/85952A2, WO 02/16382A1, WO 02/18369A2, WO 2051814A1, WO 2057287A2, WO2057425A2, WO 2060875A1, WO 2060896A1, WO 2060898A1, WO 2068058A2, WO 3020298A1, WO 3037349A1, WO 3039548A1, WO 3045901 A2, WO 3047512A2, WO 3053958A1, WO 3055447A2, WO 3059269A2, WO 3063573A2, WO 3087071 A1, WO 90/01545A1, WO 97/40028A1, WO 97/41211A1, WO 98/40381A1, and WO 99/55663A1).

[0321] 20) Leukotriene Inhibitors

[0322] In another embodiment, the pharmacologically active compound is a leukotreine inhibitor (e.g., ONO-

4057(benzenepropanoic acid, 2-(4-carboxybutoxy)-6-((6-(4-methoxyphenyl)-5-hexenyl)oxy)-, (E)-), ONO-LB-448, pirodomast 1,8-naphthyridin-2(1H)-one, 4-hydroxy-1-phenyl-3-(1-pyrrolidinyl)-, Sch-40120 (benzo(b)(1,8)naphthyridin-5(7H)-one, 10-(3-chlorophenyl)-6,8,9,10-tetrahydro-), L-656224 (4-benzofuranol, 7-chloro-2-((4-methoxyphenyl-)methyl)-3-methyl-5-propyl-), MAFP (methyl arachidonyl fluorophosphonate), ontazolast (2-benzoxazolamine, N-(2-cyclohexyl-1-(2-pyridinyl)ethyl)-5-methyl-, (S)-), amelubant (carbamic acid, ((4-((3-((4-(1-(4-hydroxyphenyl)-1-methylethyl)phenoxy)methyl)phenyl)methoxy)phenyl) iminomethyl)-ethyl ester), SB-201993 (benzoic acid, 3-((((6-((1E)-2-carboxyethenyl)-5-((8-(4-methoxypheny-l)octyl)oxy)-2-pyridinyl)methyl)thio)methyl)-), LY-203647 (ethanone, 1-(2-hydroxy-3-propyl-4-(4-(2-(4-(1H-tetrazol-5-yl)butyl)-2H-tetrazol-5-yl)butoxy)phenyl)-), LY-210073, LY-223982 (benzenepropanoic acid, 5-(3-carboxybenzoyl)-2-((6-(4-methoxyphenyl)-5-hexenyl)oxy)-, (E)-), LY-293111 (benzoic acid, 2-(3-(3-((5-ethyl-4'-fluoro-2-hydroxy(1,1'-biphenyl)-4-yl)oxy)propoxy)-2-propylphenoxy)-), SM-9064 (pyrrolidine, 1-(4,11-dihydroxy-13-(4-methoxyphenyl)-1-oxo-5,7,9-tridecatrienyl)-, (E, E, E)-), T-0757 (2,6-octadienamide, N-(4-hydroxy-3,5-dimethylphenyl)-3,7-dimethyl-, (2E)-), or an analogue or derivative thereof).

[**0323**] 21) MCP-1 Antagonists

[**0324**] In another embodiment, the pharmacologically active compound is a MCP-1 antagonist (e.g., nitronaproxen (2-napthaleneacetic acid, 6-methoxy-alpha-methyl 4-(nitrooxy)butyl ester (alpha S)-), bindarit (2-(1-benzylindazol-3-ylmethoxy)-2-methylpropanoic acid), 1-alpha-25 dihydroxy vitamin D_3, or an analogue or derivative thereof).

[**0325**] 22) MMP Inhibitors

[**0326**] In another embodiment, the pharmacologically active compound is a matrix metalloproteinase (MMP) inhibitor (e.g., D-9120, doxycycline (2-naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-(4S-(4 alpha, 4a alpha, 5 lpha, 5a alpha, 6 alpha, 12a alpha))-), BB-2827, BB-1101 (2S-allyl-N-1-hydroxy-3R-isobutyl-N-4-(1S-methylcarbamoyl-2-phenylethyl)-succinamide), BB-2983, solimastat (N'-(2,2-dimethyl-1(S)-(N-(2-pyridyl-)carbamoyl)propyl)-N4-hydroxy-2(R)-isobutyl-3(S)-methoxysuccinamide), batimastat (butanediamide, N4-hydroxy-N-1-(2-(methylamino)-2-oxo-1-(phenylmethyl)ethyl)-2-(2-methylpropyl)-3-((2-thienylthio)methyl)-, (2R-(1(S*),2R*, 3S*))-), CH-138, CH-5902, D-1927, D-5410, EF-13 (gamma-linolenic acid lithium salt), CMT-3 (2-naphthacenecarboxamide, 1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-, (4aS,5aR,12aS)-), marimastat (N-(2,2-dimethyl-1(S)-(N-methylcarbamoyl)propyl)-N, 3(S)-dihydroxy-2(R)-isobutylsuccinamide), TIMP'S,ONO-4817, rebimastat (L-Valinamide, N-((2S)-2-mercapto-1-oxo-4-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)butyl)-L-leucyl-N,3-dimethyl-), PS-508, CH-715, nimesulide (methanesulfonamide, N-(4-nitro-2-phenoxyphenyl)-), hexahydro-2-(2(R)-(1 (RS)-(hydroxycarbamoyl)-4-phenylbutyl)nonanoyl)-N-(2,2,6,6-etramethyl-4-piperidinyl)-3(S)-pyridazine carboxamide, Rs-113-080, Ro-1130830, cipemastat (1-piperidinebutanamide, 1-(cyclopentylmethyl)-N-hydroxy-gamma-oxo-alpha-((3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)methyl)-,(alpha R,βR)-), 5-(4'-biphenyl)-5-(N-(4-nitrophenyl)piperazinyl)barbituric acid, 6-methoxy-1,2,3,4-tetrahydro-norharman-1-carboxylic acid, Ro-31-4724 (L-alanine, N-(2-(2-(hydroxyamino)-2-oxoethyl)-4-methyl-1-oxopentyl)-L-leucyl-, ethyl ester), prinomastat (3-thiomorpholinecarboxamide, N-hydroxy-2,2-dimethyl-4-((4-(4-pyridinyloxy) phenyl)sulfonyl)-, (3R)-), AG-3433 (1H-pyrrole-3-propanic acid,1-(4'-cyano(1,1'-biphenyl)-4-yl)-b-((((3S)-tetrahydro-4,4-dimethyl-2-oxo-3-furanyl)amino)carbonyl)-, phenylmethyl ester, (bS)-), PNU-142769 (2H-Isoindole-2-butanamide, 1,3-dihydro-N-hydroxy-alpha-((3S)-3-(2-methylpropyl)-2-oxo-1-(2-phenylethyl)-3-pyrrolidinyl)-1,3-dioxo-, (alpha R)-), (S)-1-(2-((((4,5-dihydro-5-thioxo-1,3,4-thiadiazol-2-yl)amino)-carbonyl)amino 1-oxo-3-(pentafluorophenyl)propyl)-4-(2-pyridinyl)piperazine, SU-5402 (1H-pyrrole-3-propanoic acid, 2-((1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl)-4-methyl-), SC-77964, PNU-171829, CGS-27023A, N-hydroxy-2(R)-((4-methoxybenzene-sulfonyl)(4-picolyl)amino)-2-(2-tetrahydrofuranyl)-acetamide, L-758354 ((1,1'-biphenyl)-4-hexanoic acid, alpha-butyl-gamma-(((2,2-dimethyl-1-((methylamino)carbonyl)propyl)amino)carbonyl)-4'-fluoro-, (alpha S-(alpha R*, gammaS*(R*)))-, GI-155704A, CPA-926, TMI-005, XL-784, or an analogue or derivative thereof). Additional representative examples are included in U.S. Pat. Nos. 5,665,777; 5,985,911; 6,288,261; 5,952,320; 6,441,189; 6,235,786; 6,294,573; 6,294,539; 6,563,002; 6,071,903; 6,358,980; 5,852,213; 6,124,502; 6,160,132; 6,197,791; 6,172,057; 6,288,086; 6,342,508; 6,228,869; 5,977,408; 5,929,097; 6,498,167; 6,534,491; 6,548,524; 5,962,481; 6,197,795; 6,162,814; 6,441,023; 6,444,704; 6,462,073; 6,162,821; 6,444,639; 6,262,080; 6,486,193; 6,329,550; 6,544,980; 6,352,976; 5,968,795; 5,789,434; 5,932,763; 6,500,847; 5,925,637; 6,225,314; 5,804,581; 5,863,915; 5,859,047; 5,861,428; 5,886,043; 6,288,063; 5,939,583; 6,166,082; 5,874,473; 5,886,022; 5,932,577; 5,854,277; 5,886,024; 6,495,565; 6,642,255; 6,495,548; 6,479,502; 5,696,082; 5,700,838; 6,444,639; 6,262,080; 6,486,193; 6,329,550; 6,544,980; 6,352,976; 5,968,795; 5,789,434; 5,932,763; 6,500,847; 5,925,637; 6,225,314; 5,804,581; 5,863,915; 5,859,047; 5,861,428; 5,886,043; 6,288,063; 5,939,583; 6,166,082; 5,874,473; 5,886,022; 5,932,577; 5,854,277; 5,886,024; 6,495,565; 6,642,255; 6,495,548; 6,479,502; 5,696,082; 5,700,838; 5,861,436; 5,691,382; 5,763,621; 5,866,717; 5,902,791; 5,962,529; 6,017,889; 6,022,873; 6,022,898; 6,103,739; 6,127,427; 6,258,851; 6,310,084; 6,358,987; 5,872,152; 5,917,090; 6,124,329; 6,329,373; 6,344,457; 5,698,706; 5,872,146; 5,853,623; 6,624,144; 6,462,042; 5,981,491; 5,955,435; 6,090,840; 6,114,372; 6,566,384; 5,994,293; 6,063,786; 6,469,020; 6,118,001; 6,187,924; 6,310,088; 5,994,312; 6,180,611; 6,110,896; 6,380,253; 5,455,262; 5,470,834; 6,147,114; 6,333,324; 6,489,324; 6,362,183; 6,372,758; 6,448,250; 6,492,367; 6,380,258; 6,583,299; 5,239,078; 5,892,112; 5,773,438; 5,696,147; 6,066,662; 6,600,057; 5,990,158; 5,731,293; 6,277,876; 6,521,606; 6,168,807; 6,506,414; 6,620,813; 5,684,152; 6,451,791; 6,476,027; 6,013,649; 6,503,892; 6,420,427; 6,300,514; 6,403,644; 6,177,466; 6,569,899; 5,594,006; 6,417,229; 5,861,510; 6,156,798; 6,387,931; 6,350,907; 6,090,852; 6,458,822; 6,509,337; 6,147,061; 6,114,568; 6,118,016; 5,804,593; 5,847,153; 5,859,061; 6,194,451; 6,482,827; 6,638,952; 5,677,282; 6,365,630; 6,130,254; 6,455,569; 6,057,369; 6,576,628; 6,110,924; 6,472,396; 6,548,667; 5,618,844; 6,495,578; 6,627,411; 5,514,716; 5,256,657; 5,773,428;

6,037,472; 6,579,890; 5,932,595; 6,013,792; 6,420,415; 5,532,265; 5,691,381; 5,639,746; 5,672,598; 5,830,915; 6,630,516; 5,324,634; 6,277,061; 6,140,099; 6,455,570; 5,595,885; 6,093,398; 6,379,667; 5,641,636; 5,698,404; 6,448,058; 6,008,220; 6,265,432; 6,169,103; 6,133,304; 6,541,521; 6,624,196; 6,307,089; 6,239,288; 5,756,545; 6,020,366; 6,117,869; 6,294,674; 6,037,361; 6,399,612; 6,495,568; 6,624,177; 5,948,780; 6,620,835; 6,284,513; 5,977,141; 6,153,612; 6,297,247; 6,559,142; 6,555,535; 6,350,885; 5,627,206; 5,665,764; 5,958,972; 6,420,408; 6,492,422; 6,340,709; 6,022,948; 6,274,703; 6,294,694; 6,531,499; 6,465,508; 6,437,177; 6,376,665; 5,268,384; 5,183,900; 5,189,178; 6,511,993; 6,617,354; 6,331,563; 5,962,466; 5,861,427; 5,830,869; and 6,087,359.

[0327] 23) NF Kappa B Inhibitors

[0328] In another embodiment, the pharmacologically active compound is a NF kappa B (NFKB) inhibitor (e.g., AVE-0545, Oxi-104 (benzamide, 4-amino-3-chloro-N-(2-(diethylamino)ethyl)-), dexlipotam, R-flurbiprofen ((1,1'-biphenyl)-4-acetic acid, 2-fluoro-alpha-methyl), SP100030 (2-chloro-N-(3,5-di(trifluoromethyl)phenyl)-4-(trifluoromethyl)pyrimidine-5-carboxamide), AVE-0545, Viatris, AVE-0547, Bay 11-7082, Bay 11-7085, 15 deoxy-prostaylandin J2, bortezomib (boronic acid, ((1R)-3-methyl-1-(((2S)-1-oxo-3-phenyl-2-((pyrazinylcarbonyl)amino)propyl)amino)butyl)-, benzamide an d nicotinamide derivatives that inhibit NF-kappaB, such as those described in U.S. Pat. Nos. 5,561,161 and 5,340,565 (OxiGene), PG490-88Na, or an analogue or derivative thereof).

[0329] 24) NO antagonists

[0330] In another embodiment, the pharmacologically active compound is a NO antagonist (e.g., NCX-4016 (benzoic acid, 2-(acetyloxy)-, 3-((nitrooxy)methyl)phenyl ester, NCX-2216, L-arginine or an analogue or derivative thereof).

[0331] 25) P38 MAP Kinase Inhibitors

[0332] In another embodiment, the pharmacologically active compound is a p38 MAP kinase inhibitor (e.g., GW-2286, CGP-52411, BIRB-798, SB220025, RO-320-1195, RWJ-67657, RWJ-68354, SCIO-469, SCIO-323, AMG-548, CMC-146, SD-31145, CC-8866, Ro-320-1195, PD-98059 (4H-1-benzopyran-4-one, 2-(2-amino-3-methoxyphenyl)-), CGH-2466, doramapimod, SB-203580 (pyridine, 4-(5-(4-fluorophenyl)-2-(4-(methylsulfinyl)phenyl)-1H-imidazol-4-yl)-), SB-220025 ((5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole), SB-281832, PD169316, SB202190, GSK-681323, EO-1606, GSK-681323, or an analogue or derivative thereof). Additional representative examples are included in U.S. Pat. Nos. 6,300,347; 6,316,464; 6,316,466; 6,376,527; 6,444,696; 6,479,507; 6,509,361; 6,579,874; 6,630,485, U.S. Patent Application Publication Nos. 2001/0044538A1; 2002/0013354A1; 2002/0049220A1; 2002/0103245A1; 2002/0151491A1; 2002/0156114A1; 2003/0018051A1; 2003/0073832A1; 2003/0130257A1; 2003/0130273A1; 2003/0130319A1; 2003/0139388A1; 20030139462A1; 2003/0149031A1; 2003/0166647A1; 2003/018141A1; and PCT Publication Nos. WO 00/63204A2; WO 01/21591A1; WO 01/35959A1; WO 01/74811A2; WO 02/18379A2; WO 2064594A2; WO 2083622A2; WO 2094842A2; WO 2096426A1; WO 2101015A2; WO 2103000A2; WO 3008413A1; WO 3016248A2; WO 3020715A1; WO 3024899A2; WO 3031431A1; WO3040103A1; WO 3053940A1; WO 3053941A2; WO 3063799A2; WO 3079986A2; WO 3080024A2; WO 3082287A1; WO 97/44467A1; WO 99/01449A1; and WO 99/58523A1.

[0333] 26) Phosphodiesterase Inhibitors

[0334] In another embodiment, the pharmacologically active compound is a phosphodiesterase inhibitor (e.g., CDP-840 (pyridine, 4-((2R)-2-(3-(cyclopentyloxy)-4-methoxyphenyl)-2-phenylethyl)-), CH-3697, CT-2820, D-22888 (imidazo[1,5-a)pyrido(3,2-e)pyrazin-6(5H)-one, 9-ethyl-2-methoxy-7-methyl-5-propyl-), D-4418 (8-methoxyquinoline-5-(N-(2,5-dichloropyridin-3-yl))carboxamide), 1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(2,6-dichloro-4-pyridyl) ethanone oxime, D-4396, ONO-6126, CDC-998, CDC-801, V-11294A (3-(3-(cyclopentyloxy)-4-methoxybenzyl)-6-(ethylamino)-8-isopropyl-3H-purine hydrochloride), S,S'-methylene-bis(2-(8-cyclopropyl-3-propyl-6-(4-pyridylmethylamino)-2-thio-3H-purine)) tetrahyrochloride, rolipram (2-pyrrolidinone, 4-(3-(cyclopentyloxy)-4-methoxyphenyl)-), CP-293121, CP-353164 (5-(3-cyclopentyloxy-4-methoxyphenyl)pyridine-2-carboxamide), oxagrelate (6-phthalazinecarboxylic acid, 3,4-dihydro-1-(hydroxymethyl)-5,7-dimethyl-4-oxo-, ethyl ester), PD-168787, ibudilast (1-propanone, 2-methyl-1-(2-(1-methylethyl)pyrazolo(1,5-a)pyridin-3-yl)-), oxagrelate (6-phthalazinecarboxylic acid, 3,4-dihydro-1-(hydroxymethyl)-5,7-dimethyl-4-oxo-, ethyl ester), griseolic acid (alpha-L-talo-oct-4-enofuranuronic acid, 1-(6-amino-9H-purin-9-yl)-3,6-anhydro-6-C-carboxy-1,5-dideoxy-), KW-4490, KS-506, T-440, roflumilast (benzamide, 3-(cyclopropylmethoxy)-N-3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)-), rolipram, milrinone, triflusinal (benzoic acid, 2-(acetyloxy)-4-(trifluoromethyl)-), anagrelide hydrochloride (imidazo[2,1-b)quinazolin-2(3H)-one, 6,7-dichloro-1,5-dihydro-, monohydrochloride), cilostazol (2(1H)-quinolinone, 6-(4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy)-3,4-dihydro-), propentofylline (1H-purine-2,6-dione, 3,7-dihydro-3-methyl-1-(5-oxohexyl)-7-propyl-), sildenafil citrate (piperazine, 1-((3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo(4,3-d)pyrimidin-5-yl)-4-ethoxyphenyl)sulfonyl)-4-methyl, 2-hydroxy-1,2,3-propanetricarboxylate-(1:1)), tadalafil (pyrazino(1',2',6)pyrido(3,4-b)indole1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R-trans)), vardenafil (piperazine, 1-(3-(1,4-dihydro-5-methyl(−4-oxo-7-propylimidazo[5,1-f)(1,2,4)-triazin-2-yl)-4-ethoxyphenyl)sulfonyl)-4-ethyl-), milrinone ((3,4'-bipyridine)-5-carbonitrile, 1,6-dihydro-2-methyl-6-oxo-), enoximone (2H-imidazol-2-one, 1,3-dihydro-4-methyl-5-(4-(methylthio)benzoyl)-), theophylline (1H-purine-2,6-dione, 3,7-dihydro-1,3-dimethyl-), ibudilast (1-propanone, 2-methyl-1-(2-(1-methylethyl)pyrazolo(1,5-a)pyridin-3-yl)-), aminophylline (1H-purine-2,6-dione, 3,7-dihydro-1,3-dimethyl-, compound with 1,2-ethanediamine (2:1)-), acebrophylline (7H-purine-7-acetic acid, 1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-,compd. with trans-4-(((2-amino-3,5-dibromophenyl)methyl)amino)cyclohexanol (1:1)), plafibride (propanamide, 2-(4-chlorophenoxy)-2-methyl-N-(((4-morpholinylmethyl)amino)carbonyl)-), ioprinone hydrochloride (3-pyridinecarbonitrile, 1,2-dihydro-5-imidazo[1,2-a)pyridin-6-yl-6-methyl-2-oxo-, monohydrochloride-), fosfosal (benzoic acid, 2-(phosphonooxy)-), amrinone ((3,4'-bipyridin)-6(1H)-one, 5-amino-, or an analogue or derivative thereof).

[0335] Other examples of phosphodiesterase inhibitors include denbufylline (1H-purine-2,6-dione, 1,3-dibutyl-3,7-dihydro-7-(2-oxopropyl)-), propentofylline (1H-purine-2,6-dione, 3,7-dihydro-3-methyl-1-(5-oxohexyl)-7-propyl-) and pelrinone (5-pyrimidinecarbonitrile, 1,4-dihydro-2-methyl-4-oxo-6-[(3-pyridinylmethyl)amino]-).

[0336] Other examples of phosphodiesterase III inhibitors include enoximone (2H-imidazol-2-one, 1,3-dihydro-4-methyl-5-[4-(methylthio)benzoyl]-), and saterinone (3-pyridinecarbonitrile, 1,2-dihydro-5-[4-[2-hydroxy-3-[4-(2-methoxyphenyl)-1-piperazinyl]propoxy]phenyl]-6-methyl-2-oxo-).

[0337] Other examples of phosphodiesterase IV inhibitors include AWD-12-281, 3-auinolinecarboxylic acid, 1-ethyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-), tadalafil (pyrazino(1',2':1,6)pyrido(3,4-b)indole1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R-trans)), and filaminast (ethanone, 1-[3-(cyclopentyloxy)-4-methoxyphenyl]-, 0-(aminocarbonyl)oxime, (1E)-).

[0338] Another example of a phosphodiesterase V inhibitor is vardenafil (piperazine, 1-(3-(1,4-dihydro-5-methyl(-4-oxo-7-propylimidazo[5,1-f)(1,2,4)-triazin-2-yl)-4-ethoxyphenyl)sulfonyl)-4-ethyl-).

[0339] 27) TGF Beta Inhibitors

[0340] In another embodiment, the pharmacologically active compound is a TGF beta Inhibitor (e.g., mannose-6-phosphate, LF-984, tamoxifen (ethanamine, 2-(4-(1,2-diphenyl-1-butenyl)phenoxy)-N,N-dimethyl-, (Z)-), tranilast, or an analogue or derivative thereof).

[0341] 28) Thromboxane A2 Antagonists

[0342] In another embodiment, the pharmacologically active compound is a thromboxane A2 antagonist (e.g., CGS-22652 (3-pyridineheptanoic acid, γ-(4-(((4-chlorophenyl)sulfonyl)amino)butyl)-, (.+−.)-), ozagrel (2-propenoic acid, 3-(4-(1H-imidazol-1-ylmethyl)phenyl)-, (E)-), argatroban (2-piperidinecarboxylic acid, 1-(5-((aminoiminomethyl)amino)-1-oxo-2-(((1,2,3,4-tetrahydro-3-methyl-8-quinolinyl)sulfonyl)amino)pentyl)-4-methyl-), ramatroban (9H-carbazole-9-propanoic acid, 3-(((4-fluorophenyl)sulfonyl)amino)-1,2,3,4-tetrahydro-, (R)-), torasemide (3-pyridinesulfonamide, N-(((1-methylethyl)amino)carbonyl)-4-((3-methylphenyl)amino)-), gamma linoleic acid ((Z,Z,Z)-6,9,12-octadecatrienoic acid), seratrodast (benzeneheptanoic acid, zeta-(2,4,5-trimethyl-3,6-dioxo-1,4-cyclohexadien-1-yl)-, (+/−)-, or an analogue or derivative thereof).

[0343] 29) TNF alpha Antagonists and TACE Inhibitors

[0344] In another embodiment, the pharmacologically active compound is a TNF alpha antagonist or TACE inhibitor (e.g., E-5531 (2-deoxy-6-O-(2-deoxy-3-O-(3(R)-(5(Z)-dodecenoyloxy)-decyl)-6-O-methyl-2-(3-oxotetradecanamido)-4-β-phosphono-β-D-glucopyranosyl)-3-O-(3(R)-hydroxydecyl)-2-(3-oxotetradecanamido)-alpha-D-glucopyranose-1-O-phosphate), AZD-4717, glycophosphopeptical, UR-12715 (B=benzoic acid, 2-hydroxy-5-((4-(3-(4-(2-methyl-1H-imidazol(4,5-c)pyridin-1-yl)methyl)-1-piperidinyl)-3-oxo-1-phenyl-1-propenyl)phenyl)azo) (Z)), PMS-601, AM-87, xyloadenosine (9H-purin-6-amine, 9-β-D-xylofuranosyl-), RDP-58, RDP-59, BB2275, benzydamine, E-3330 (undecanoic acid, 2-((4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)methylene)-, (E)-), N-(D,L-2-(hydroxyaminocarbonyl)methyl-4-methylpentanoyl)-L-3-(2'-naphthyl)alanyl-L-alanine, 2-aminoethyl amide, CP-564959, MLN-608, SPC-839, ENMD-0997, Sch-23863 ((2-(10,11-dihydro-5-ethoxy-5H-dibenzo (a,d) cyclohepten-S-yl)-N,N-dimethyl-ethanamine), SH-636, PKF-241-466, PKF-242-484, TNF-484A, cilomilast (cis-4-cyano-4-(3-(cyclopentyloxy)-4-methoxyphenyl)cyclohexane-1-carboxylic acid), GW-3333, GW-4459, BMS-561392, AM-87, cloricromene (acetic acid, ((8-chloro-3-(2-(diethylamino)ethyl)-4-methyl-2-oxo-2H-1-benzopyran-7-yl)oxy)-, ethyl ester), thalidomide (1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)-), vesnarinone (piperazine, 1-(3,4-dimethoxybenzoyl)-4-(1,2,3,4-tetrahydro-2-oxo-6-quinolinyl)-), infliximab, lentinan, etanercept (1-235-tumor necrosis factor receptor (human) fusion protein with 236-467-immunoglobulin G1 (human gamma1-chain Fc fragment)), diacerein (2-anthracenecarboxylic acid, 4,5-bis(acetyloxy)-9,10-dihydro-9,10-dioxo-, or an analogue or derivative thereof).

[0345] 30) Tyrosine Kinase Inhibitors

[0346] In another embodiment, the pharmacologically active compound is a tyrosine kinase inhibitor (e.g., SKI-606, ER-068224, SD-208, N-(6-benzothiazolyl)-4-(2-(1-piperazinyl)pyrid-5-yl)-2-pyrimidineamine, celastrol (24,25,26-trinoroleana-1(10),3,5,7-tetraen-29-oic acid, 3-hydroxy-9,13-dimethyl-2-oxo-, (9 beta.,13alpha,14β,20 alpha)-), CP-127374 (geldanamycin, 17-demethoxy-17-(2-propenylamino)-), CP-564959, PD-171026, CGP-52411 (1H-Isoindole-1,3(2H)-dione, 4,5-bis(phenylamino)-), CGP-53716 (benzamide, N-(4-methyl-3-((4-(3-pyridinyl)-2-pyrimidinyl)amino)phenyl)-), imatinib (4-((methyl-1-piperazinyl)methyl)-N-(4-methyl-3-((4-(3-pyridinyl)-2-pyrimidinyl)amino]phenyl)benzamide methanesulfonate), NVP-MK980-NX, KF-250706 (13-chloro,5(R),6(S)-epoxy-14,16-dihydroxy-11-(hydroyimino)-3(R)-methyl-3,4,5,6,11,12-hexahydro-1H-2-benzoxacyclotetradecin-1-one), 5-(3-(3-methoxy-4-(2-((E)-2-phenylethenyl)-4-oxazolylmethoxy)phenyl)propyl)-3-(2-((E)-2-phenylethenyl)-4-oxazolylmethyl)-2,4-oxazolidinedione, genistein, NV-06, or an analogue or derivative thereof).

[0347] 31) Vitronectin Inhibitors

[0348] In another embodiment, the pharmacologically active compound is a vitronectin inhibitor (e.g., O-(9,10-dimethoxy-1,2,3,4,5,6-hexahydro-4-((1,4,5,6-tetrahydro-2-pyrimidinyl)hydrazono)-8-benz(e)azulenyl)-N-((phenylmethoxy)carbonyl)-DL-homoserine 2,3-dihydroxypropyl ester, (2S)-benzoylcarbonylamino-3-(2-((4S)-(3-(4,5-dihydro-1H-imidazol-2-ylamino)-propyl)-2,5-dioxo-imidazolidin-1-yl)-acetylamino)-propionate, Sch-221153, S-836, SC-68448 (β-((2-2-(((3-((aminoiminomethyl)amino)-phenyl)carbonyl)amino)acetyl)amino)-3,5-dichlorobenzenepropanoic acid), SD-7784, S-247, or an analogue or derivative thereof).

[0349] 32) Fibroblast Growth Factor Inhibitors

[0350] In another embodiment, the pharmacologically active compound is a fibroblast growth factor inhibitor (e.g., CT-052923 (((2H-benzo(d)1,3-dioxalan-5-methyl)amino)(4-(6,7-dimethoxyquinazolin-4-yl)piperazinyl-)methane-1-thione), or an analogue or derivative thereof).

[0351] 33) Protein Kinase Inhibitors

[0352] In another embodiment, the pharmacologically active compound is a protein kinase inhibitor (e.g., KP-0201448, NPC15437 (hexanamide, 2,6-diamino-N-((1-(1-oxotridecyl)-2-piperidinyl)methyl)-), fasudil (1H-1,4-diazepine, hexahydro-1-(5-isoquinolinylsulfonyl)-), midostaurin (benzamide, N-(2,3,10,11,12,13-hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1H,9H-diindolo(1,2,3-gh:3',2',1'-lm)pyrrolo(3,4-j)(1,7)benzodiazonin-11-yl)-N-methyl-, (9Alpha,10β,11β,13Alpha)-),fasudil (1H-1,4-diazepine, hexahydro-1-(5-isoquinolinylsulfonyl)-, dexniguldipine (3,5-pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-, 3-(4,4-diphenyl-1-piperidinyl)propyl methyl ester, monohydrochloride, (R)-), LY-317615 (1H-pyrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, monohydrochloride), perifosine (piperidinium, 4-[[hydroxy(octadecyloxy)phosphinyl]oxy]-1,1-dimethyl-, inner salt), LY-333531 (9H,18H-5,21:12,17-dimethenodibenzo(e,k)pyrrolo(3,4-h)(1,4,13)oxadiazacyclohexadecine-18,20(19H)-dione,9-((dimethylamino)methyl)-6,7,10,11-tetrahydro-, (S)-), Kynac; SPC-100270 (1,3-octadecanediol, 2-amino-, [S-(R*,R*)]-), Kynacyte, or an analogue or derivative thereof).

[0353] 34) PDGF Receptor Kinase Inhibitors

[0354] In another embodiment, the pharmacologically active compound is a PDGF receptor kinase inhibitor (e.g., RPR-127963E, or an analogue or derivative thereof).

[0355] 35) Endothelial Growth Factor Receptor Kinase Inhibitors

[0356] In another embodiment, the pharmacologically active compound is an endothelial growth factor receptor kinase inhibitor (e.g., CEP-7055, SU-0879 ((E)-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-(aminothiocarbonyl)acrylonitrile), BIBF-1000, AG-013736 (CP-868596), AMG-706, AVE-0005, NM-3 (3-(2-methylcarboxymethyl)-6-methoxy-8-hydroxy-isocoumarin), Bay-43-9006, SU-011248, or an analogue or derivative thereof).

[0357] 36) Retinoic Acid Receptor Antagonists

[0358] In another embodiment, the pharmacologically active compound is a retinoic acid receptor antagonist (e.g., etarotene (Ro-15-1570) (naphthalene, 6-(2-(4-(ethylsulfonyl)phenyl)-1-methylethenyl)-1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-, (E)-), (2E,4E)-3-methyl-5-(2-((E)-2-(2,6,6-trimethyl-1-cyclohexen-1-yl)ethenyl)-1-cyclohexen-1-yl)-2,4-pentadienoic acid, tocoretinate (retinoic acid, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl ester, (2R*(4R*,8R*))-(±)-), aliretinoin (retinoic acid, cis-9, trans-13-), bexarotene (benzoic acid, 4-(1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)ethenyl)-), tocoretinate (retinoic acid, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl ester, [2R*(4R*,8R*)]-(±)-, or an analogue or derivative thereof).

[0359] 37) Platelet Derived Growth Factor Receptor Kinase Inhibitors

[0360] In another embodiment, the pharmacologically active compound is a platelet derived growth factor receptor kinase inhibitor (e.g., leflunomide (4-isoxazolecarboxamide, 5-methyl-N-(4-(trifluoromethyl)phenyl)-, or an analogue or derivative thereof).

[0361] 38) Fibrinogen Antagonists

[0362] In another embodiment, the pharmacologically active compound is a fibrinogin antagonist (e.g., picotamide (1,3-benzenedicarboxamide, 4-methoxy-N,N'-bis(3-pyridinylmethyl)-, or an analogue or derivative thereof).

[0363] 39) Antimycotic Agents

[0364] In another embodiment, the pharmacologically active compound is an antimycotic agent (e.g., miconazole, sulconizole, parthenolide, rosconitine, nystatin, isoconazole, fluconazole, ketoconasole, imidazole, itraconazole, terpinafine, elonazole, bifonazole, clotrimazole, conazole, terconazole (piperazine, 1-(4-((2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl)methoxy)phenyl)-4-(1-methylethyl)-, cis-), isoconazole (1-(2-(2-6-dichlorobenzyloxy)-2-(2-,4-dichlorophenyl-)ethyl)), griseofulvin (spiro(benzofuran-2(3H), 1'-(2)cyclohexane)-3,4'-dione, 7-chloro-2',4,6-trimeth-oxy-6'methyl-, (1'S-trans)-), bifonazole (1H-imidazole, 1-((1,1'-biphenyl)-4-ylphenylmethyl)-), econazole nitrate (1-(2-((4-chlorophenyl)methoxy)-2-(2,4-dichlorophenyl)ethyl)-1H-imidazole nitrate), croconazole (1H-imidazole, 1-(1-(2-((3-chlorophenyl)methoxy)phenyl)ethenyl)-), sertaconazole (1H-Imidazole, 1-(2-((7-chlorobenzo(b)thien-3-yl)methoxy)-2-(2,4-dichlorophenyl)ethyl)-), omoconazole (1H-imidazole, 1-(2-(2-(4-chlorophenoxy)ethoxy)-2-(2,4-dichlorophenyl)-1-methylethenyl)-, (Z)-), flutrimazole (1H-imidazole, 1-((2-fluorophenyl)(4-fluorophenyl)phenylmethyl)-), fluconazole (1H-1,2,4-triazole-1-ethanol, alpha-(2,4-difluorophenyl)-alpha-(1H-1,2,4-triazol-1-ylmethyl)-), neticonazole (1H-Imidazole, 1-(2-(methylthio)-1-(2-(pentyloxy)phenyl)ethenyl)-, monohydrochloride, (E)-), butoconazole (1H-imidazole, 1-(4-(4-chlorophenyl)-2-((2,6-dichlorophenyl)thio)butyl)-, (+/−)-), clotrimazole (1-((2-chlorophenyl)diphenylmethyl)-1H-imidazole, or an analogue or derivative thereof).

[0365] 40) Bisphosphonates

[0366] In another embodiment, the pharmacologically active compound is a bisphosphonate (e.g., clodronate, alendronate, pamidronate, zoledronate, or an analogue or derivative thereof).

[0367] 41) Phospholipase A1 Inhibitors

[0368] In another embodiment, the pharmacologically active compound is a phospholipase A1 inhibitor (e.g., ioteprednol etabonate (androsta-1,4-diene-17-carboxylic acid, 17-((ethoxycarbonyl)oxy)-11-hydroxy-3-oxo-, chloromethyl ester, (11β,17 alpha)-, or an analogue or derivative thereof).

[0369] 42) Histamine H1/H2/H3 Receptor Antagonists

[0370] In another embodiment, the pharmacologically active compound is a histamine H1, H2, or H3 receptor

antagonist (e.g., ranitidine (1,1-ethenediamine, N-(2-(((5-((dimethylamino)methyl)$_2$-furanyl)methyl)thio)ethyl)-N'-methyl-2-nitro-), niperotidine (N-(2-((5-((dimethylamino)methyl)furfuryl)thio)ethyl)-2-nitro-N'-piperonyl-1,1-ethenediamine), famotidine (propanimidamide, 3-(((2-((aminoiminomethyl)amino)-4-thiazolyl)methyl)thio)-N-(aminosulfonyl)-), roxitadine acetate HCl (acetamide, 2-(acetyloxy)-N-(3-(3-(1-piperidinylmethyl)phenoxy)propyl)-, monohydrochloride), lafutidine (acetamide, 2-((2-furanylmethyl)sulfinyl)-N-(4-((4-(1-piperidinylmethyl)-2-pyridinyl)oxy)-2-butenyl)-, (Z)-), nizatadine (1,1-ethenediamine, N-(2-(((2-((dimethylamino)methyl)-4-thiazolyl)methyl)thio)ethyl)-N'-methyl-2-nitro-), ebrotidine (benzenesulfonamide, N-(((2-(((2-((aminoiminomethyl)amino)-4-thiazoly)methyl)thio)ethyl)amino)methylene)-4-bromo-), rupatadine (5H-benzo(5,6)cyclohepta(1,2-b)pyridine, 8-chloro-6,11-dihydro-11-(1-((5-methyl-3-pyridinyl)methyl)-4-piperidinylidene)-, trihydrochloride-), fexofenadine HCl (benzeneacetic acid, 4-(1-hydroxy-4-(4(hydroxydiphenylmethyl)-1-piperidinyl)butyl)-alpha, alpha-dimethyl-, hydrochloride, or an analogue or derivative thereof).

[0371] 43) Macrolide Antibiotics

[0372] In another embodiment, the pharmacologically active compound is a macrolide antibiotic (e.g., dirithromycin (erythromycin, 9-deoxo-11-deoxy-9,11-(imino(2-(2-methoxyethoxy)ethylidene)oxy)-, (9S(R))-), flurithromycin ethylsuccinate (erythromycin, 8-fluoro-mono(ethyl butanedioate) (ester)-), erythromycin stinoprate (erythromycin, 2'-propanoate, compound with N-acetyl-L-cysteine (1:1)), clarithromycin (erythromycin, 6-O-methyl-), azithromycin (9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin-A), telithromycin (3-de((2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)oxy)-11,12-dideoxy-6-O-methyl-3-oxo-12,11-(oxycarbonyl((4-(4-(3-pyridinyl)-1H-imidazol-1-yl)butyl)imino))-), roxithromycin (erythromycin, 9-(O-((2-methoxyethoxy)methyl)oxime)), rokitamycin (leucomycin V, 4B-butanoate 3B-propanoate), RV-11 (erythromycin monopropionate mercaptosuccinate), midecamycin acetate (leucomycin V, 3B,9-diacetate 3,4B-dipropanoate), midecamycin (leucomycin V, 3,4B-dipropanoate), josamycin (leucomycin V, 3-acetate 4B-(3-methylbutanoate), or an analogue or derivative thereof).

[0373] 44) GPIIb IIIa Receptor Antagonists

[0374] In another embodiment, the pharmacologically active compound is a GPIIb IIIa receptor antagonist (e.g., tirofiban hydrochloride (L-tyrosine, N-(butylsulfonyl)-O-(4-(4-piperidinyl)butyl)-, monohydrochloride-), eptifibatide (L-cysteinamide, N6-(aminoiminomethyl)-N-2-(3-mercapto-1-oxopropyl)-L-lysylglycyl-L-alpha-aspartyl-L-tryptophyl-L-prolyl-, cyclic(1->6)-disulfide), xemilofiban hydrochloride, or an analogue or derivative thereof).

[0375] 45) Endothelin Receptor Antagonists

[0376] In another embodiment, the pharmacologically active compound is an endothelin receptor antagonist (e.g., bosentan (benzenesulfonamide, 4-(1,1-dimethylethyl)-N-(6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)(2,2'-bipyrimidin)-4-yl)-, or an analogue or derivative thereof).

[0377] 46) Peroxisome Proliferator-Activated Receptor Agonists

[0378] In another embodiment, the pharmacologically active compound is a peroxisome proliferator-activated receptor agonist (e.g., gemfibrozil (pentanoic acid, 5-(2,5-dimethylphenoxy)-2,2-dimethyl-), fenofibrate (propanoic acid, 2-(4-(4-chlorobenzoyl)phenoxy)-2-methyl-, 1-methylethyl ester), ciprofibrate (propanoic acid, 2-(4-(2,2-dichlorocyclopropyl)phenoxy)-2-methyl-), rosiglitazone maleate (2,4-thiazolidinedione, 5-((4-(2-(methyl-2-pyridinylamino-)ethoxy)phenyl)methyl)-, (Z)-2-butenedioate (1:1)), pioglitazone hydrochloride (2,4-thiazolidinedione, 5-((4-(2-(5-ethyl-2-pyridinyl)ethoxy)phenyl)methyl)-, monohydrochloride (+/−)-), etofylline clofibrate (propanoic acid, 2-(4-chlorophenoxy)-2-methyl-, 2-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-7H-purin-7-yl)ethyl ester), etofibrate (3-pyridinecarboxylic acid, 2-(2-(4-chlorophenoxy)-2-methyl-1-oxopropoxy)ethyl ester), clinofibrate (butanoic acid, 2,2'-(cyclohexylidenebis(4,1-phenyleneoxy))bis(2-methyl-)), bezafibrate (propanoic acid, 2-(4-(2-((4-chlorobenzoyl)amino)ethyl)phenoxy)-2-methyl-), binifibrate (3-pyridinecarboxylic acid, 2-(2-(4-chlorophenoxy)-2-methyl-1-oxopropoxy)-1,3-propanediyl ester), or an analogue or derivative thereof).

[0379] In one aspect, the pharmacologically active compound is a peroxisome proliferator-activated receptor alpha agonist, such as GW-590735, GSK-677954, GSK501516, pioglitazone hydrochloride (2,4-thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-, monohydrochloride (+/−)-, or an analogue or derivative thereof).

[0380] 47) Estrogen Receptor Agents

[0381] In another embodiment, the pharmacologically active compound is an estrogen receptor agent (e.g., estradiol, 17-β-estradiol, or an analogue or derivative thereof).

[0382] 48) Somatostatin Analogues

[0383] In another embodiment, the pharmacologically active compound is a somatostatin analogue (e.g., angiopeptin, or an analogue or derivative thereof).

[0384] 49) Neurokinin 1 Antagonists

[0385] In another embodiment, the pharmacologically active compound is a neurokinin 1 antagonist (e.g., GW-597599, lanepitant ((1,4'-bipiperidine)-1'-acetamide, N-(2-(acetyl((2-methoxyphenyl)methyl)amino)-1-(1H-indol-3-ylmethyl)ethyl](R)-), nolpitantium chloride (1-azoniabicyclo[2.2.2]octane, 1-[2-[3-(3,4-dichlorophenyl)-1-[[3-(1-methylethoxy)phenyl]acetyl]-3-piperidinyl]ethyl]-4-phenyl-, chloride, (S)-), or saredutant (benzamide, N-[4-[4-(acetylamino)-4-phenyl-1-piperidinyl]-2-(3,4-dichlorophenyl)butyl]-N-methyl-, (S)-), or vofopitant (3-piperidinamine, N-[[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]phenyl]methyl]-2-phenyl-, (2S,3S)-, or an analogue or derivative thereof).

[0386] 50) Neurokinin 3 Antagonist

[0387] In another embodiment, the pharmacologically active compound is a neurokinin 3 antagonist (e.g., talnetant (4-quinolinecarboxamide, 3-hydroxy-2-phenyl-N-[(1S)-1-phenylpropyl]-, or an analogue or derivative thereof).

[0388] 51) Neurokinin Antagonist

[0389] In another embodiment, the pharmacologically active compound is a neurokinin antagonist (e.g., GSK-679769, GSK-823296, SR-489686 (benzamide, N-[4-[4-(acetylamino)-4-phenyl-1-piperidinyl]-2-(3,4-dichlorophenyl)butyl]-N-methyl-, (S)-), SB-223412; SB-235375 (4-quinolinecarboxamide, 3-hydroxy-2-phenyl-N-[(1S)-1-phenylpropyl]-), UK-226471, or an analogue or derivative thereof).

[0390] 52) VLA-4 Antagonist

[0391] In another embodiment, the pharmacologically active compound is a VLA-4 antagonist (e.g., GSK683699, or an analogue or derivative thereof).

[0392] 53) Osteoclast Inhibitor

[0393] In another embodiment, the pharmacologically active compound is a osteoclast inhibitor (e.g., ibandronic acid (phosphonic acid, [1-hydroxy-3-(methylpentylamino-)propylidene]bis-), alendronate sodium, or an analogue or derivative thereof).

[0394] 54) DNA topoisomerase ATP Hydrolysing Inhibitor

[0395] In another embodiment, the pharmacologically active compound is a DNA topoisomerase ATP hydrolysing inhibitor (e.g., enoxacin (1,8-naphthyridine-3-carboxylic acid, 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-), levofloxacin (7H-Pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid, 9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-, (S)-), ofloxacin (7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid, 9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-, (+/−)-), pefloxacin (3-quinolinecarboxylic acid, 1-ethyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-), pipemidic acid (pyrido[2,3-d]pyrimidine-6-carboxylic acid, 8-ethyl-5,8-dihydro-5-oxo-2-(1-piperazinyl)-), pirarubicin (5,12-naphthacenedione, 10-[[3-amino-2,3,6-trideoxy-4-O-(tetrahydro-2H-pyran-2-yl)-alpha-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, [8S-[8 alpha,10 alpha(S*)]]-), sparfloxacin (3-quinolinecarboxylic acid, 5-amino-1-cyclopropyl-7-(3,5-dimethyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxo-, cis-), AVE-6971, cinoxacin ([1,3]dioxolo[4,5-g]cinnoline-3-carboxylic acid, 1-ethyl-1,4-dihydro-4-oxo-), or an analogue or derivative thereof).

[0396] 55) Angiotensin I Converting Enzyme Inhibitor

[0397] In another embodiment, the pharmacologically active compound is an angiotensin I converting enzyme inhibitor (e.g., ramipril (cyclopenta[b]pyrrole-2-carboxylic acid, 1-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, [2S-[1[R*(R*)],2 alpha,3aβ,6aβ]]-), trandolapril (1H-indole-2-carboxylic acid, 1-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]octahydro-, [2S-[1[R*(R*)],2 alpha,3a alpha,7aβ]]-), fasidotril (L-alanine, N-[(2S)-3-(acetylthio)-2-(1,3-benzodioxol-5-ylmethyl)-1-oxopropyl]-, phenylmethyl ester), cilazapril (6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid, 9-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]octahydro-10-oxo-, [1S-[1 alpha, 9 alpha(R*)]]-), ramipril (cyclopenta[b]pyrrole-2-carboxylic acid, 1-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, [2S-[1 [R*(R*)], 2 alpha, 3aβ,6aβ]]-, or an analogue or derivative thereof).

[0398] 56) Angiotensin II Antagonist

[0399] In another embodiment, the pharmacologically active compound is an angiotensin II antagonist (e.g., HR-720 (1H-imidazole-5-carboxylic acid, 2-butyl-4-(methylthio)-1-[[2'-[[[(propylamino)carbonyl]amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-, dipotassium salt, or an analogue or derivative thereof).

[0400] 57) Enkephalinase Inhibitor

[0401] In another embodiment, the pharmacologically active compound is an enkephalinase inhibitor (e.g., Aventis 100240 (pyrido[2,1-a][2]benzazepine-4-carboxylic acid, 7-[[2-(acetylthio)-1-oxo-3-phenylpropyl]amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-, [4S-[4 alpha, 7 alpha(R*), 12bβ]]-), AVE-7688, or an analogue or derivative thereof).

[0402] 58) Peroxisome Proliferator-Activated Receptor Gamma Agonist Insulin Sensitizer

[0403] In another embodiment, the pharmacologically active compound is peroxisome proliferator-activated receptor gamma agonist insulin sensitizer (e.g., rosiglitazone maleate (2,4-thiazolidinedione, 5-((4-(2-(methyl-2-pyridinylamino)ethoxy)phenyl)methyl)-, (Z)-2-butenedioate (1:1), farglitazar (GI-262570, GW-2570, GW-3995, GW-5393, GW-9765), LY-929, LY-519818, LY-674, or LSN-862), or an analogue or derivative thereof).

[0404] 59) Protein Kinase C Inhibitor

[0405] In another embodiment, the pharmacologically active compound is a protein kinase C inhibitor, such as ruboxistaurin mesylate (9H,18H-5,21:12,17-dimethenodibenzo(e,k)pyrrolo(3,4-h)(1,4,13)oxadiazacyclohexadecine-18,20(19H)-dione,9-((dimethylamino)methyl)-6,7,10,11-tetrahydro-, (S)-), safingol (1,3-octadecanediol, 2-amino-, [S-(R*,R*)]-), or enzastaurin hydrochloride (1H-pyrole-2,5-dione, 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1H-indol-3-yl]-, monohydrochloride), or an analogue or derivative thereof.

[0406] 60) ROCK (rho-Associated Kinase) Inhibitors

[0407] In another embodiment, the pharmacologically active compound is a ROCK (rho-associated kinase) inhibitor, such as Y-27632, HA-1077, H-1152 and 4-1-(aminoalkyl)-N-(4-pyridyl) cyclohexanecarboxamide or an analogue or derivative thereof.

[0408] 61) CXCR3 Inhibitors

[0409] In another embodiment, the pharmacologically active compound is a CXCR3 inhibitor such as T-487, T0906487 or analogue or derivative thereof.

[0410] 62) ltk Inhibitors

[0411] In another embodiment, the pharmacologically active compound is an ltk inhibitor such as BMS-509744 or an analogue or derivative thereof.

[0412] 63) Cytosolic Phospholipase A_2-Alpha Inhibitors

[0413] In another embodiment, the pharmacologically active compound is a cytosolic phospholipase A_2-alpha inhibitor such as efipladib (PLA-902) or analogue or derivative thereof.

[0414] 64) PPAR Agonist

[0415] In another embodiment, the pharmacologically active compound is a PPAR Agonist (e.g., Metabolex ((−)-benzeneacetic acid, 4-chloro-alpha-[3-(trifluoromethyl)-phenoxy]-, 2-(acetylamino)ethyl ester), balaglitazone (5-(4-(3-methyl-4-oxo-3,4-dihydro-quinazolin-2-yl-methoxy)-benzyl)-thiazolidine-2,4-dione), ciglitazone (2,4-thiazolidinedione, 5-[[4-[(1-methylcyclohexyl)methoxy] phenyl]methyl]-), DRF-10945, farglitazar, GSK-677954, GW-409544, GW-501516, GW-590735, GW-590735, K-111, KRP-101, LSN-862, LY-519818, LY-674, LY-929, muraglitazar; BMS-298585 (Glycine, N-[(4-methoxyphenoxy)carbonyl]-N-[[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]methyl]-), netoglitazone; isaglitazone (2,4-thiazolidinedione, 5-[[6-[(2-fluorophenyl)methoxy]-2-naphthalenyl]methyl]-), Actos AD-4833; U-72107A (2,4-thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy] phenyl]methyl]-, monohydrochloride (+/−)-), JTT-501; PNU-182716 (3,5-Isoxazolidinedione, 4-[[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]methyl]-), AVANDIA (from SB Pharmco Puerto Rico, Inc. (Puerto Rico); BRL-48482;BRL-49653;BRL-49653c; NYRACTA and Venvia (both from (SmithKline Beecham (United Kingdom)); tesaglitazar ((2S)-2-ethoxy-3-[4-[2-[4-[(methylsulfonyl)oxy] phenyl]ethoxy]phenyl]propanoic acid), troglitazone (2,4-Thiazolidinedione, 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl] methyl]-), and analogues and derivatives thereof).

[0416] 65) Immunosuppressants

[0417] In another embodiment, the pharmacologically active compound is an immunosuppressant (e.g., batebulast (cyclohexanecarboxylic acid, 4-[[(aminoiminomethyl)amino]methyl]-, 4-(1,1-dimethylethyl)phenyl ester, trans-), cyclomunine, exalamide (benzamide, 2-(hexyloxy)-), LYN-001, CCl-779 (rapamycin 42-(3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate)), 1726; 1726-D; AVE-1726, or an analogue or derivative thereof).

[0418] 66) Erb Inhibitor

[0419] In another embodiment, the pharmacologically active compound is an Erb inhibitor (e.g., canertinib dihydrochloride (N-[4-(3-(chloro-4-fluoro-phenylamino)-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-yl]-acrylamide dihydrochloride), CP-724714, or an analogue or derivative thereof).

[0420] 67) Apoptosis Agonist

[0421] In another embodiment, the pharmacologically active compound is an apoptosis agonist (e.g., CEFLATONIN (CGX-635) (from Chemgenex Therapeutics, Inc., Menlo Park, Calif.), CHML, LBH-589, metoclopramide (benzamide, 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy-), patupilone (4,17-dioxabicyclo(14.1.0)heptadecane-5,9-dione, 7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl, (1R,3S,7S,10R,11S,12S,16R)), AN-9; pivanex (butanoic acid, (2,2-dimethyl-1-oxopropoxy)methyl ester), SL-100; SL-102; SL-11093; SL-11098; SL-11099; SL-93; SL-98; SL-99, or an analogue or derivative thereof).

[0422] 68) Lipocortin Agonist

[0423] In another embodiment, the pharmacologically active compound is an lipocortin agonist (e.g., CGP-13774 (9Alpha-chloro-6Alpha-fluoro-11β,17alpha-dihydroxy-16Alpha-methyl-3-oxo-1,4-androstadiene-17'-carboxylic acid-methylester-17-propionate), or analogue or derivative thereof).

[0424] 69) VCAM-1 Antagonist

[0425] In another embodiment, the pharmacologically active compound is a VCAM-1 antagonist (e.g., DW-908e, or an analogue or derivative thereof).

[0426] 70) Collagen Antagonist

[0427] In another embodiment, the pharmacologically active compound is a collagen antagonist (e.g., E-5050 (Benzenepropanamide, 4-(2,6-dimethylheptyl)-N-(2-hydroxyethyl]-β-methyl-), lufironil (2,4-Pyridinedicarboxamide, N,N'-bis(2-methoxyethyl)-), or an analogue or derivative thereof).

[0428] 71) Alpha 2 Integrin Antagonist

[0429] In another embodiment, the pharmacologically active compound is an alpha 2 integrin antagonist (e.g., E-7820, or an analogue or derivative thereof).

[0430] 72) TNF Alpha Inhibitor

[0431] In another embodiment, the pharmacologically active compound is a TNF alpha inhibitor (e.g., ethyl pyruvate, Genz-29155, lentinan (Ajinomoto Co., Inc. (Japan)), linomide (3-quinolinecarboxamide, 1,2-dihydro-4-hydroxy-N,1-dimethyl-2-oxo-N-phenyl-), UR-1505, or an analogue or derivative thereof).

[0432] 73) Nitric Oxide Inhibitor

[0433] In another embodiment, the pharmacologically active compound is a nitric oxide inhibitor (e.g., guanidioethyldisulfide, or an analogue or derivative thereof).

[0434] 74) Cathepsin Inhibitor

[0435] In another embodiment, the pharmacologically active compound is a cathepsin inhibitor (e.g., SB-462795 or an analogue or derivative thereof).

[0436] Combination Therapies

[0437] In addition to incorporation of a fibrosis-inhibiting agent, one or more other pharmaceutically active agents can be incorporated into the present compositions to improve or enhance efficacy. In one aspect, the composition may further include a compound which acts to have an inhibitory effect on pathological processes in or around the treatment site. Representative examples of additional therapeutically active agents include, by way of example and not limitation, anti-thrombotic agents, anti-proliferative agents, anti-inflammatory agents, neoplastic agents, enzymes, receptor antagonists or agonists, hormones, antibiotics, antimicrobial agents, antibodies, cytokine inhibitors, IMPDH (inosine monophosplate dehydrogenase) inhibitors tyrosine kinase inhibitors, MMP inhibitors, p38 MAP kinase inhibitors, immunosuppressants, apoptosis antagonists, caspase inhibitors, and JNK inhibitors.

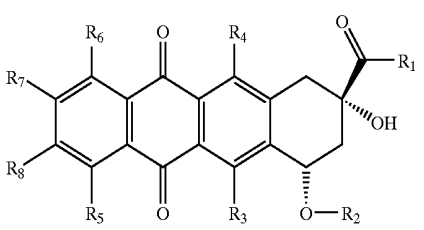
[0438] In one aspect, the present invention also provides for the combination of an electrical device (as well as compositions and methods for making electrical devices) that includes an anti-fibrosing agent and an anti-infective agent, which reduces the likelihood of infections.

[0439] Infection is a common complication of the implantation of foreign bodies such as, for example, medical devices. Foreign materials provide an ideal site for microorganisms to attach and colonize. It is also hypothesized that there is an impairment of host defenses to infection in the microenvironment surrounding a foreign material. These factors make medical implants particularly susceptible to infection and make eradication of such an infection difficult, if not impossible, in most cases.

[0440] The present invention provides agents (e.g., chemotherapeutic agents) that can be released from a composition, and which have potent antimicrobial activity at extremely low doses. A wide variety of anti-infective agents can be utilized in combination with the present compositions. Suitable anti-infective agents may be readily determined based the assays provided in Example 56. Discussed in more detail below are several representative examples of agents that can be used: (A) anthracyclines (e.g., doxorubicin and mitoxantrone), (B) fluoropyrimidines (e.g., 5-FU), (C) folic acid antagonists (e.g., methotrexate), (D) podophylotoxins (e.g., etoposide), (E) camptothecins, (F) hydroxyureas, and (G) platinum complexes (e.g., cisplatin).

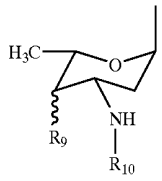
[0441] a) Anthracyclines

[0442] Anthracyclines have the following general structure, where the R groups may be a variety of organic groups:



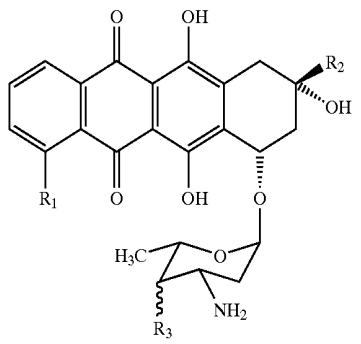
[0443] According to U.S. Pat. No. 5,594,158, suitable R groups are as follows: R_1 is CH_3 or CH_2OH; R_2 is daunosamine or H; R_3 and R_4 are independently one of OH, NO_2, NH_2, F, Cl, Br, I, CN, H or groups derived from these; R_5 is hydrogen, hydroxyl, or methoxy; and R_{6-8} are all hydrogen. Alternatively, R_5 and R_6 are hydrogen and R_7 and R_8 are alkyl or halogen, or vice versa.

[0444] According to U.S. Pat. No. 5,843,903, R_1 may be a conjugated peptide. According to U.S. Pat. No. 4,296,105, R_5 may be an ether linked alkyl group. According to U.S. Pat. No. 4,215,062, R_5 may be OH or an ether linked alkyl group. R_1 may also be linked to the anthracycline ring by a group other than C(O), such as an alkyl or branched alkyl group having the C(O) linking moiety at its end, such as $—CH_2CH(CH_2—X)C(O)—R_1$, wherein X is H or an alkyl group (see, e.g., U.S. Pat. No. 4,215,062). R_2 may alternately be a group linked by the functional group =N—NHC(O)—Y, where Y is a group such as a phenyl or substituted phenyl ring. Alternately R_3 may have the following structure:



[0445] in which R_9 is OH either in or out of the plane of the ring, or is a second sugar moiety such as R_3. R_{10} may be H or form a secondary amine with a group such as an aromatic group, saturated or partially saturated 5 or 6 membered heterocyclic having at least one ring nitrogen (see U.S. Pat. No. 5,843,903). Alternately, R_{10} may be derived from an amino acid, having the structure $—C(O)CH(NHR_{11})(R_{12})$, in which R_{11} is H, or forms a C_{3-4} membered alkylene with R_{12}. R_{12} may be H, alkyl, aminoalkyl, amino, hydroxyl, mercapto, phenyl, benzyl or methylthio (see U.S. Pat. No. 4,296,105).

[0446] Exemplary anthracyclines are doxorubicin, daunorubicin, idarubicin, epirubicin, pirarubicin, zorubicin, and carubicin. Suitable compounds have the structures:



	R_1	R_2	R_3
Doxorubicin:	OCH_3	$C(O)CH_2OH$	OH out of ring plane
Epirubicin:			

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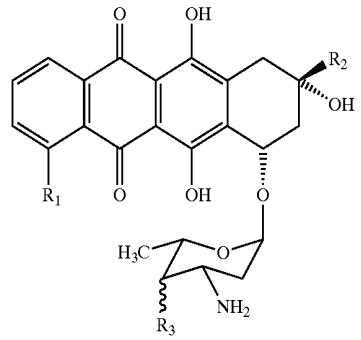

	R_1	R_2	R_3
(4' epimer of doxo-rubicin)	OCH_3	$C(O)CH_2OH$	OH in ring plane
Dauno-rubicin:	OCH_3	$C(O)CH_3$	OH out of ring plane
Ida-rubicin:	H	$C(O)CH_3$	OH out of ring plane

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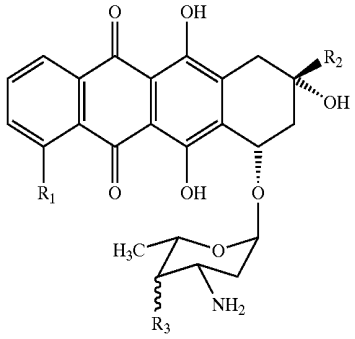
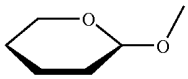
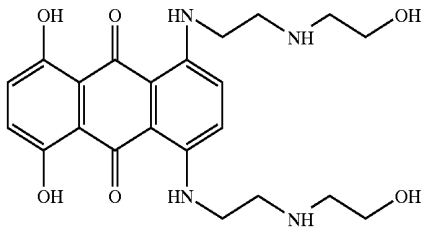


	R_1	R_2	R_3
Pira-rubicin:	OCH_3	$C(O)CH_2OH$	
Zorubicin:	OCH_3	$C(CH_3)(=N)NHC(O)C_6H_5$	OH
Carubicin:	OH	$C(O)CH_3$	OH out of ring plane

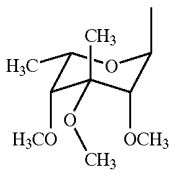
[**0447**] Other suitable anthracyclines are anthramycin, mitoxantrone, menogaril, nogalamycin, aclacinomycin A, olivomycin A, chromomycin A_3, and plicamycin having the structures:



Mitoxantrone

	R_1	R_2	R_3
Menogaril	H	OCH_3	H
Nogalamycin	O-sugar	H	$COOCH_3$

sugar:



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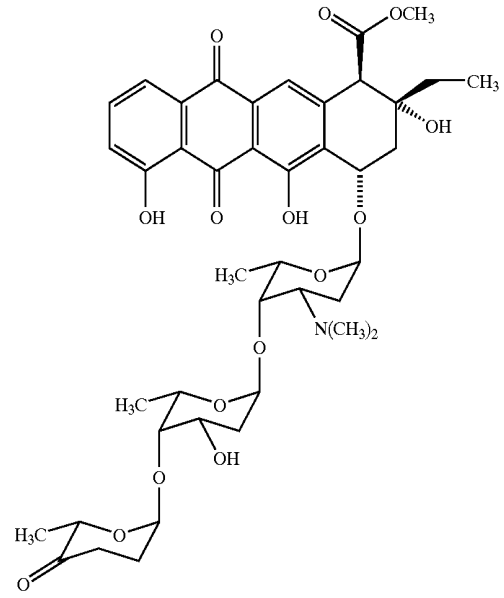
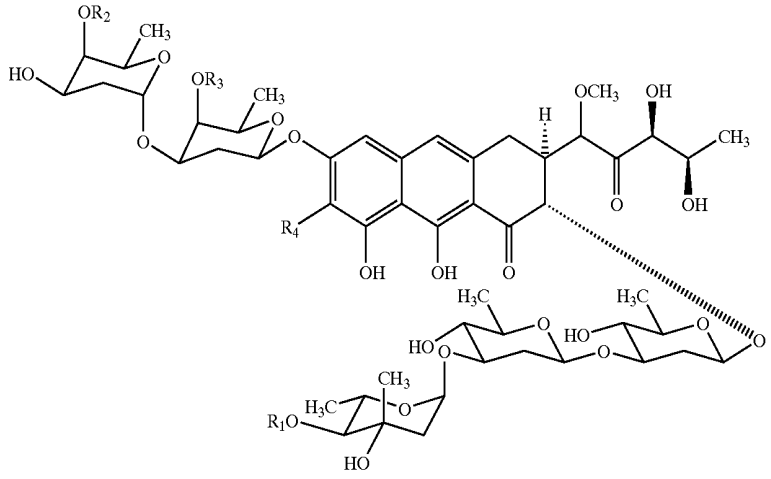


Aclacinomycin A



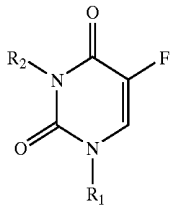
	R_1	R_2	R_3	R_4
Olivomycin A	$COCH(CH_3)_2$	CH_3	$COCH_3$	H
Chromomycin A_3	$COCH_3$	CH_3	$COCH_3$	CH_3
Plicamycin	H	H	H	CH_3

[0448] Other representative anthracyclines include, FCE 23762, a doxorubicin derivative (Quaglia et al., *J. Liq. Chromatogr.* 17(18):3911-3923, 1994), annamycin (Zou et al., *J. Pharm. Sci.* 82(11):1151-1154, 1993), ruboxyl (Rapoport et al., *J. Controlled Release* 58(2):153-162, 1999), anthracycline disaccharide doxorubicin analogue (Pratesi et al., *Clin. Cancer Res.* 4(11):2833-2839, 1998), N-(trifluoroacetyl)doxorubicin and 4'-O-acetyl-N-(trifluoroacetyl-)doxorubicin (Berube & Lepage, *Synth. Commun.* 28(6):1109-1116, 1998), 2-pyrrolinodoxorubicin (Nagy et al., *Proc. Nat'l Acad. Sci. U.S.A.* 95(4):1794-1799, 1998), disaccharide doxorubicin analogues (Arcamone et al., *J. Nat'l Cancer Inst.* 89(16): 1217-1223,1997), 4-demethoxy-7-O-[2,6-dideoxy-4-O-(2,3,6-trideoxy-3-amino-α-L-lyxo-hexopyranosyl)-α-L-lyxo-hexopyranosyl]-adriamicinone doxorubicin disaccharide analogue (Monteagudo et al., *Carbohydr. Res.* 300(1):11-16, 1997), 2-pyrrolinodoxorubicin (Nagy et al., *Proc. Nat'l Acad. Sci. U.S.A.* 94(2):652-656, 1997), morpholinyl doxorubicin analogues (Duran et al., *Cancer Chemother. Pharmacol.* 38(3):210-216, 1996), enaminomalonyl-β-alanine doxorubicin derivatives (Seitz et al., *Tetrahedron Lett.* 36(9):1413-16, 1995), cephalosporin doxorubicin derivatives (Vrudhula et al., *J. Med. Chem.* 38(8):1380-5, 1995), hydroxyrubicin (Solary et al., *Int. J. Cancer* 58(1):85-94, 1994), methoxymorpholino doxorubicin derivative (Kuhl et al., *Cancer Chemother. Pharmacol.* 33(1): 10-16, 1993), (6-maleimidocaproyl)hydrazone doxorubicin derivative (Willner et al., *Bioconjugate Chem.* 4(6):521-7, 1993), N-(5,5-diacetoxypent-1-yl) doxorubicin (Cherif & Farquhar, *J. Med. Chem.* 35(17):3208-14, 1992),

FCE 23762 methoxymorpholinyl doxorubicin derivative (Ripamonti et al., *Br. J. Cancer* 65(5):703-7, 1992), N-hydroxysuccinimide ester doxorubicin derivatives (Demant et al., *Biochim. Biophys. Acta* 1118(1):83-90, 1991), polydeoxynucleotide doxorubicin derivatives (Ruggiero et al., *Biochim. Biophys. Acta* 1129(3):294-302, 1991), morpholinyl doxorubicin derivatives (EPA 434960), mitoxantrone doxorubicin analogue (Krapcho et al., *J. Med. Chem.* 34(8):2373-80. 1991), AD198 doxorubicin analogue (Traganos et al., *Cancer Res.* 51(14):3682-9, 1991), 4-demethoxy-3'-N-trifluoroacetyldoxorubicin (Horton et al., *Drug Des. Delivery* 6(2):123-9, 1990), 4'-epidoxorubicin (Drzewoski et al., *Pol. J. Pharmacol. Pharm.* 40(2):159-65, 1988; Weenen et al., *Eur. J. Cancer Clin. Oncol.* 20(7):919-26, 1984), alkylating cyanomorpholino doxorubicin derivative (Scudder et al., *J. Nat'l Cancer Inst.* 80(16):1294-8, 1988), deoxydihydroiodooxorubicin (EPA 275966), adriblastin (Kalishevskaya et al., *Vestn. Mosk. Univ.,* 16(Biol. 1):21-7, 1988), 4'-deoxydoxorubicin (Schoelzel et al., *Leuk. Res.* 10(12):1455-9, 1986), 4-demethyoxy-4'-o-methyldoxorubicin (Giuliani et al., *Proc. Int. Congr. Chemother.* 16:285-70-285-77, 1983), 3'-deamino-3'-hydroxydoxorubicin (Horton et al., *J. Antibiot.* 37(8):853-8, 1984), 4-demethyoxy doxorubicin analogues (Barbieri et al., *Drugs Exp. Clin. Res.* 10(2):85-90, 1984), N-L-leucyl doxorubicin derivatives (Trouet et al., Anthracyclines (*Proc. Int. Symp. Tumor Pharmacother.*), 179-81, 1983), 3'-deamino-3'-(4-methoxy-1-piperidinyl) doxorubicin derivatives (U.S. Pat. No. 4,314,054), 3'-deamino-3'-(4-mortholinyl) doxorubicin derivatives (U.S. Pat. No. 4,301,277), 4'-deoxydoxorubicin and 4'-o-methyldoxorubicin (Giuliani et al., *Int. J. Cancer* 27(1):5-13,1981), aglycone doxorubicin derivatives (Chan & Watson, *J. Pharm. Sci.* 67(12):1748-52,1978), SM 5887 (Pharma Japan 1468:20, 1995), MX-2 (*Pharma Japan* 1420:19, 1994), 4'-deoxy-13(S)-dihydro-4'-iododoxorubicin (EP 275966), morpholinyl doxorubicin derivatives (EPA 434960), 3'-deamino-3'-(4-methoxy-1-piperidinyl) doxorubicin derivatives (U.S. Pat. No. 4,314,054), doxorubicin-14-valerate, morpholinodoxorubicin (U.S. Pat. No. 5,004,606), 3'-deamino-3'-(3"-cyano-4"-morpholinyl doxorubicin; 3'-deamino-3'-(3"-cyano-4"-morpholinyl)-13-dihydoxorubicin; (3'-deamino-3'-(3"-cyano-4"-morpholinyl) daunorubicin; 3'-deamino-3'-(3"-cyano-4"-morpholinyl)-3-dihydrodaunorubicin; and 3'-deamino-3'-(4"-morpholinyl-5-iminodoxorubicin and derivatives (U.S. Pat. No. 4,585,859), 3'-deamino-3'-(4-methoxy-1-piperidinyl) doxorubicin derivatives (U.S. Pat. No. 4,314,054) and 3-deamino-3-(4-morpholinyl) doxorubicin derivatives (U.S. Pat. No. 4,301, 277).

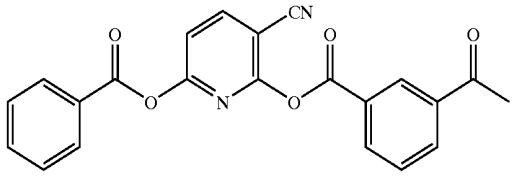
[**0449**] b) Fluoropyrimidine Analogues

[**0450**] In another aspect, the therapeutic agent is a fluoropyrimidine analog, such as 5-fluorouracil, or an analogue or derivative thereof, including carmofur, doxifluridine, emitefur, tegafur, and floxuridine. Exemplary compounds have the structures:



	R_1	R_2
5-Fluorouracil	H	H
Carmofur	$C(O)NH(CH_2)_5CH_3$	H
Doxifluridine	A_1	H
Floxuridine	A_2	H
Emitefur	$CH_2OCH_2CH_3$	B
Tegafur	C	H

B



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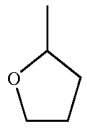
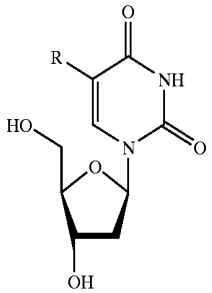


[**0451**] Other suitable fluoropyrimidine analogues include 5-FudR (5-fluoro-deoxyuridine), or an analogue or derivative thereof, including 5-iododeoxyuridine (5-IudR), 5-bromodeoxyuridine (5-BudR), fluorouridine triphosphate (5-FUTP), and fluorodeoxyuridine monophosphate (5-dFUMP). Exemplary compounds have the structures:



5-Fluoro-2'-deoxyuridine: R = F
5-Bromo-2'-deoxyuridine: R = Br
5-Iodoo-2'-deoxyuridine: R = I

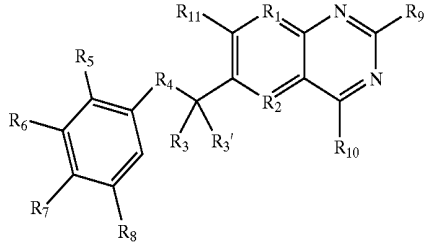
[**0452**] Other representative examples of fluoropyrimidine analogues include N3-alkylated analogues of 5-fluorouracil (Kozai et al., *J. Chem. Soc., Perkin Trans.* 1(19):3145-3146, 1998), 5-fluorouracil derivatives with 1,4-oxaheteroepane

moieties (Gomez et al., *Tetrahedron* 54(43):13295-13312, 1998), 5-fluorouracil and nucleoside analogues (Li, *Anticancer Res.* 17(1A):21-27, 1997), cis- and trans-5-fluoro-5,6-dihydro-6-alkoxyuracil (Van der Wilt et al., *Br. J. Cancer* 68(4):702-7, 1993), cyclopentane 5-fluorouracil analogues (Hronowski & Szarek, *Can. J. Chem.* 70(4):1162-9, 1992), A-OT-fluorouracil (Zhang et al., *Zongguo Yiyao Gongye Zazhi* 20(11):513-15, 1989), N4-trimethoxybenzoyl-5'-deoxy-5-fluorocytidine and 5'-deoxy-5-fluorouridine (Miwa et al., *Chem. Pharm. Bull.* 38(4):998-1003, 1990), 1-hexylcarbamoyl-5-fluorouracil (Hoshi et al., *J. Pharmacobio-Dun.* 3(9):478-81, 1980; Maehara et al., *Chemotherapy* (Basel) 34(6):484-9,1988), B-3839 (Prajda et al., *In Vivo* 2(2):151-4, 1988), uracil-1-(2-tetrahydrofuryl)-5-fluorouracil (Anai et al., *Oncology* 45(3):144-7, 1988), 1-(2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)-5-fluorouracil (Suzuko et al., *Mol. Pharmacol.* 31(3):301-6, 1987), doxifluridine (Matuura et al., *Oyo Yakuri* 29(5):803-31, 1985), 5'-deoxy-5-fluorouridine (Bollag & Hartmann, *Eur. J. Cancer* 16(4):427-32,1980),1-acetyl-3-O-toluyl-5-fluorouracil (Okada, *Hiroshima J. Med. Sci.* 28(1):49-66, 1979), 5-fluorouracil-m-formylbenzene-sulfonate (JP 55059173), N'-(2-furanidyl)-5-fluorouracil (JP 53149985) and 1-(2-tetrahydrofuryl)-5-fluorouracil (JP 52089680).

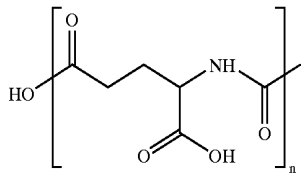
[0453] These compounds are believed to function as therapeutic agents by serving as antimetabolites of pyrimidine.

[0454] c) Folic Acid Antagonists

[0455] In another aspect, the therapeutic agent is a folic acid antagonist, such as methotrexate or derivatives or analogues thereof, including edatrexate, trimetrexate, raltitrexed, piritrexim, denopterin, tomudex, and pteropterin. Methotrexate analogues have the following general structure:

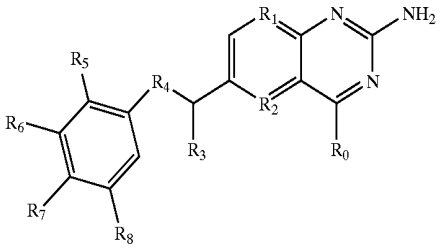


[0456] The identity of the R group may be selected from organic groups, particularly those groups set forth in U.S. Pat. Nos. 5,166,149 and 5,382,582. For example, R_1 may be N, R_2 may be N or $C(CH_3)$, R_3 and R_3' may H or alkyl, e.g., CH_3, R_4 may be a single bond or NR, where R is H or alkyl group. $R_{5,6,8}$ may be H, OCH_3, or alternately they can be halogens or hydro groups. R_7 is a side chain of the general structure:



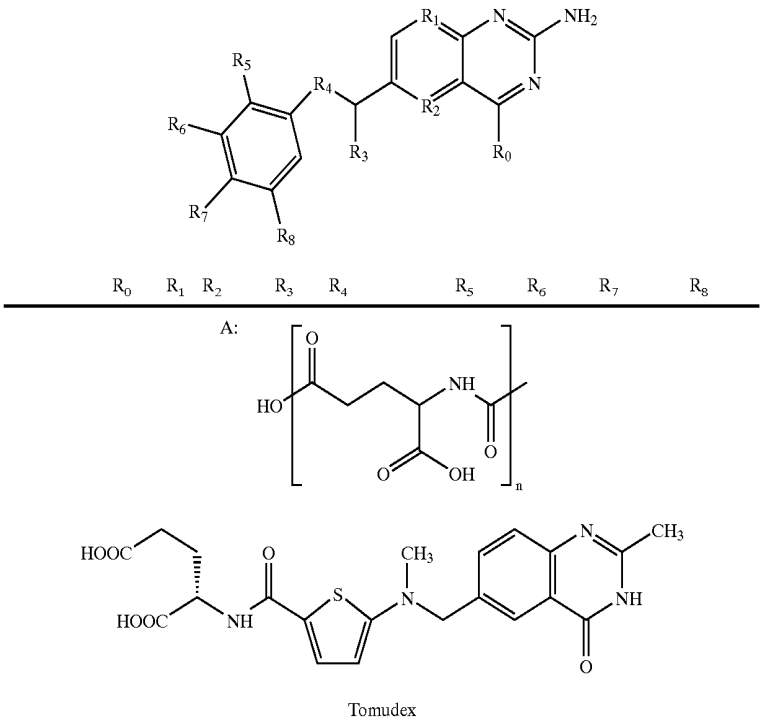
[0457] wherein n=1 for methotrexate, n=3 for pteropterin. The carboxyl groups in the side chain may be esterified or form a salt such as a Zn^{2+} salt. R_9 and R_{10} can be NH_2 or may be alkyl substituted.

[0458] Exemplary folic acid antagonist compounds have the structures:



	R_0	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
Methotrexate	NH_2	N	N	H	$N(CH_3)$	H	H	A (n = 1)	H
Edatrexate	NH_2	N	N	H	$CH(CH_2CH_3)$	H	H	A (n = 1)	H
Trimetrexate	NH_2	CH	$C(CH_3)$	H	NH	H	OCH_3	OCH_3	OCH_3
Pteropterin	OH	N	N	H	NH	H	H	A (n = 3)	H
Denopterin	OH	N	N	CH_3	$N(CH_3)$	H	H	A (n = 1)	H
Peritrexim	NH_2	N	$C(CH_3)$	H	single bond	OCH_3	H	H	OCH_3

-continued



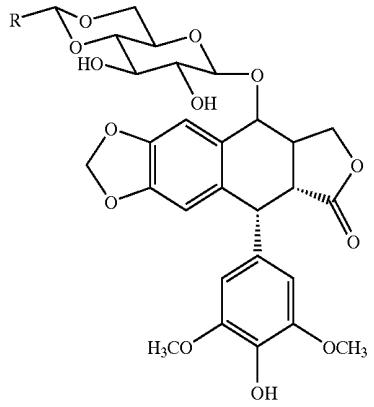
[0459] Other representative examples include 6-S-aminoacyloxymethyl mercaptopurine derivatives (Harada et al., *Chem. Pharm. Bull.* 43(10):793-6, 1995), 6-mercaptopurine (6-MP) (Kashida et al., *Biol. Pharm. Bull.* 18(11):1492-7, 1995), 7,8-polymethyleneimidazo-1,3,2-diazaphosphorines (Nilov et al., *Mendeleev Commun.* 2:67, 1995), azathioprine (Chifotides et al., *J. Inorg. Biochem.* 56(4):249-64, 1994), methyl-D-glucopyranoside mercaptopurine derivatives (Da Silva et al., *Eur. J. Med. Chem.* 29(2):149-52,1994) and s-alkynyl mercaptopurine derivatives (Ratsino et al., *Khim.-Farm. Zh.* 15(8):65-7, 1981); indoline ring and a modified ornithine or glutamic acid-bearing methotrexate derivatives (Matsuoka et al., *Chem. Pharm. Bull.* 45(7):1146-1150, 1997), alkyl-substituted benzene ring C bearing methotrexate derivatives (Matsuoka et al., *Chem. Pharm. Bull.* 44(12):2287-2293, 1996), benzoxazine or benzothiazine moiety-bearing methotrexate derivatives (Matsuoka et al., *J. Med. Chem.* 40(1):105-111, 1997), 10-deazaminopterin analogues (DeGraw et al., *J. Med. Chem.* 40(3):370-376, 1997), 5-deazaminopterin and 5,10-dideazaminopterin methotrexate analogues (Piper et al., *J. Med. Chem.* 40(3):377-384, 1997), indoline moiety-bearing methotrexate derivatives (Matsuoka et al., *Chem. Pharm. Bull.* 44(7):1332-1337, 1996), lipophilic amide methotrexate derivatives (Pignatello et al., *World Meet. Pharm. Biopharm. Pharm. Technol.,* 563-4,1995), L-threo-(2S,4S)-4-fluoroglutamic acid and DL-3,3-difluoroglutamic acid-containing methotrexate analogues (Hart et al., *J. Med. Chem.* 39(1):56-65, 1996), methotrexate tetrahydroquinazoline analogue (Gangjee, et al., *J. Heterocycl. Chem.* 32(1):243-8, 1995), N-(α-aminoacyl) methotrexate derivatives (Cheung et al., *Pteridines* 3(1-2):101-2, 1992), biotin methotrexate derivatives (Fan et al., *Pteridines* 3(1-2):131-2, 1992), D-glutamic acid or D-erythrou, threo-4-fluoroglutamic acid methotrexate analogues (McGuire et al., *Biochem. Pharmacol.* 42(12):2400-3, 1991), β,γ-methano methotrexate analogues (Rosowsky et al., *Pteridines* 2(3):133-9, 1991), 10-deazaminopterin (10-EDAM) analogue (Braakhuis et al., *Chem. Biol. Pteridines, Proc. Int. Symp. Pteridines Folic Acid Deriv.,* 1027-30, 1989), γ-tetrazole methotrexate analogue (Kalman et al., *Chem. Biol. Pteridines, Proc. Int. Symp. Pteridines Folic Acid Deriv.,* 1154-7, 1989), N-(L-α-aminoacyl) methotrexate derivatives (Cheung et al., *Heterocycles* 28(2):751-8, 1989), meta and ortho isomers of aminopterin (Rosowsky et al., *J. Med. Chem.* 32(12):2582, 1989), hydroxymethyl-methotrexate (DE 267495), γ-fluoromethotrexate (McGuire et al., *Cancer Res.* 49(16):4517-25, 1989), polyglutamyl methotrexate derivatives (Kumar et al., *Cancer Res.* 46(10):5020-3, 1986), gem-diphosphonate methotrexate analogues (WO 88/06158), α- and γ-substituted methotrexate analogues (Tsushima et al., *Tetrahedron* 44(17):5375-87, 1988), 5-methyl-5-deaza methotrexate analogues (4,725,687), Nδ-acyl-Nα-(4-amino-4-deoxypteroyl)-L-ornithine derivatives (Rosowsky et al., *J. Med. Chem.* 31(7):1332-7, 1988), 8-deaza methotrexate analogues (Kuehl et al., *Cancer Res.* 48(6):1481-8, 1988), acivicin methotrexate analogue (Rosowsky et al., *J. Med. Chem.* 30(8):1463-9, 1987), polymeric platinol methotrexate derivative (Carraher et al., *Polym. Sci. Technol.* (*Plenum*), 35(*Adv. Biomed. Polym.*):311-24, 1987), methotrexate-γ-dimyristoylphophatidylethanolamine (Kinsky et al., *Biochim. Biophys. Acta* 917(2):211-18, 1987), methotrexate polyglutamate analogues (Rosowsky et al., Chem. Biol. Pteridines, Pteridines Folic Acid Deriv., Proc. Int. Symp. Pteridines Folic Acid Deriv.: Chem., Biol. Clin. Aspects: 985-8,1986), poly-γ-glutamyl methotrexate derivatives (Kisliuk et al., Chem. Biol. Pteridines, Pteridines Folic Acid Deriv., Proc. Int. Symp. Pteridines Folic Acid Deriv.: Chem.,

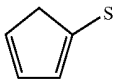
Biol. Clin. Aspects: 989-92, 1986), deoxyuridylate methotrexate derivatives (Webber et al., Chem. Biol. Pteridines, Pteridines Folic Acid Deriv., Proc. Int. Symp. Pteridines Folic Acid Deriv.: Chem., Biol. Clin. Aspects: 659-62, 1986), iodoacetyl lysine methotrexate analogue (Delcamp et al., Chem. Biol. Pteridines, Pteridines Folic Acid Deriv., Proc. Int. Symp. Pteridines Folic Acid Deriv.: Chem., Biol. Clin. Aspects: 807-9, 1986), 2,.omega.-diaminoalkanoid acid-containing methotrexate analogues (McGuire et al., *Biochem. Pharmacol.* 35(15):2607-13, 1986), polyglutamate methotrexate derivatives (Kamen & Winick, *Methods Enzymol.* 122(Vitam. Coenzymes, Pt. G):339-46, 1986), 5-methyl-5-deaza analogues (Piper et al., *J. Med. Chem.* 29(6):1080-7, 1986), quinazoline methotrexate analogue (Mastropaolo et al., *J. Med. Chem.* 29(1):155-8, 1986), pyrazine methotrexate analogue (Lever & Vestal, *J. Heterocycl. Chem.* 22(1):5-6, 1985), cysteic acid and homocysteic acid methotrexate analogues (4,490,529), γ-tert-butyl methotrexate esters (Rosowsky et al., *J. Med. Chem.* 28(5):660-7, 1985), fluorinated methotrexate analogues (Tsushima et al., *Heterocycles* 23(1):45-9, 1985), folate methotrexate analogue (Trombe, *J. Bacteriol.* 160(3):849-53, 1984), phosphonoglutamic acid analogues (Sturtz & Guillamot, *Eur. J. Med. Chem.—Chim. Ther.* 19(3):267-73, 1984), poly (L-lysine) methotrexate conjugates (Rosowsky et al., *J. Med. Chem.* 27(7):888-93, 1984), dilysine and trilysine methotrexate derivates (Forsch & Rosowsky, *J. Org. Chem.* 49(7):1305-9, 1984), 7-hydroxymethotrexate (Fabre et al., *Cancer Res.* 43(10):4648-52, 1983), poly-γ-glutamyl methotrexate analogues (Piper & Montgomery, *Adv. Exp. Med. Biol.,* 163(*Folyl Antifolyl Polyglutamates*):95-100, 1983), 3',5'-dichloromethotrexate (Rosowsky & Yu, *J. Med. Chem.* 26(10):1448-52,1983), diazoketone and chloromethylketone methotrexate analogues (Gangjee et al., *J. Pharm. Sci.* 71(6):717-19, 1982), 10-propargylaminopterin and alkyl methotrexate homologs (Piper et al., *J. Med. Chem.* 25(7):877-80, 1982), lectin derivatives of methotrexate (Lin et al., *JNCI* 66(3):523-8, 1981), polyglutamate methotrexate derivatives (Galivan, *Mol. Pharmacol.* 17(1):105-10, 1980), halogentated methotrexate derivatives (Fox, *JNCI* 58(4):J955-8, 1977), 8-alkyl-7,8-dihydro analogues (Chaykovsky et al., *J. Med. Chem.* 20(10):J1323-7, 1977), 7-methyl methotrexate derivatives and dichloromethotrexate (Rosowsky & Chen, *J. Med. Chem.* 17(12):J1308-11,1974), lipophilic methotrexate derivatives and 3',5'-dichloromethotrexate (Rosowsky, *J. Med. Chem.* 16(10):J1190-3, 1973), deaza amethopterin analogues (Montgomery et al., *Ann. N.Y. Acad. Sci.* 186:J227-34, 1971), MX068 (Pharma Japan, 1658:18, 1999) and cysteic acid and homocysteic acid methotrexate analogues (EPA 0142220);

[**0460**] These compounds are believed to act as antimetabolites of folic acid.

[**0461**] d) Podophyllotoxins

[**0462**] In another aspect, the therapeutic agent is a podophyllotoxin, or a derivative or an analogue thereof. Exemplary compounds of this type are etoposide or teniposide, which have the following structures:



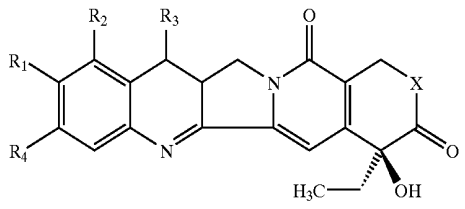
	R
Etoposide	CH_3
Teniposide	

[**0463**] Other representative examples of podophyllotoxins include Cu(II)-VP-16 (etoposide) complex (Tawa et al., *Bioorg. Med. Chem.* 6(7):1003-1008, 1998), pyrrolecarboxamidino-bearing etoposide analogues (Ji et al., *Bioorg. Med. Chem. Lett.* 7(5):607-612, 1997), 4β-amino etoposide analogues (Hu, University of North Carolina Dissertation, 1992), γ-lactone ring-modified arylamino etoposide analogues (Zhou et al., *J. Med. Chem.* 37(2):287-92, 1994), N-glucosyl etoposide analogue (Allevi et al., *Tetrahedron Leff.* 34(45):7313-16, 1993), etoposide A-ring analogues (Kadow et al., *Bioorg. Med. Chem. Lett.* 2(1):17-22,1992), 4'-deshydroxy-4'-methyl etoposide (Saulnier et al., *Bioorg. Med. Chem. Lett.* 2(10):1213-18, 1992), pendulum ring etoposide analogues (Sinha et al., *Eur. J. Cancer* 26(5):590-3, 1990) and E-ring desoxy etoposide analogues (Saulnier et al., *J. Med. Chem.* 32(7):1418-20,1989).

[**0464**] These compounds are believed to act as topoisomerase II inhibitors and/or DNA cleaving agents.

[**0465**] e) Camptothecins

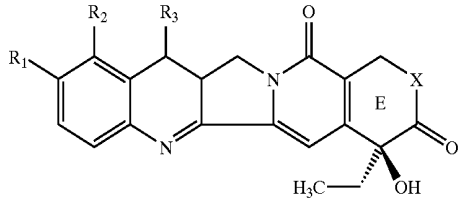
[**0466**] In another aspect, the therapeutic agent is camptothecin, or an analogue or derivative thereof. Camptothecins have the following general structure.



[**0467**] In this structure, X is typically O, but can be other groups, e.g., NH in the case of 21-lactam derivatives. R_1 is typically H or OH, but may be other groups, e.g., a terminally hydroxylated C_{1-3} alkane. R_2 is typically H or an amino

containing group such as $(CH_3)_2NHCH_2$, but may be other groups e.g., NO_2, NH_2, halogen (as disclosed in, e.g., U.S. Pat. No. 5,552,156) or a short alkane containing these groups. R_3 is typically H or a short alkyl such as C_2H_5. R_4 is typically H but may be other groups, e.g., a methylenedioxy group with R_1.

[0468] Exemplary camptothecin compounds include topotecan, irinotecan (CPT-11), 9-aminocamptothecin, 21-lactam-20(S)-camptothecin, 10,11-methylenedioxycamptothecin, SN-38, 9-nitrocamptothecin, 10-hydroxycamptothecin. Exemplary compounds have the structures:



	R_1	R_2	R_3
Camptothecin:	H	H	H
Topotecan:	OH	$(CH_3)_2NHCH_2$	H
SN-38:	OH	H	C_2H_5

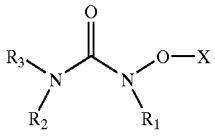
X: O for most analogs, NH for 21-lactam analogs

[0469] Camptothecins have the five rings shown here. The ring labeled E must be intact (the lactone rather than carboxylate form) for maximum activity and minimum toxicity.

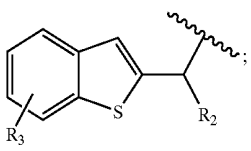
[0470] Camptothecins are believed to function as topoisomerase I inhibitors and/or DNA cleavage agents.

[0471] f) Hydroxyureas

[0472] The therapeutic agent of the present invention may be a hydroxyurea. Hydroxyureas have the following general structure:



[0473] Suitable hydroxyureas are disclosed in, for example, U.S. Pat. No. 6,080,874, wherein R_1 is:

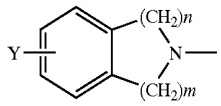


[0474] and R_2 is an alkyl group having 1-4 carbons and R_3 is one of H, acyl, methyl, ethyl, and mixtures thereof, such as a methylether.

[0475] Other suitable hydroxyureas are disclosed in, e.g., U.S. Pat. No. 5,665,768, wherein R_1 is a cycloalkenyl group, for example N-[3-[5-(4-fluorophenylthio)-furyl]-2-cyclopenten-1-yl]N-hydroxyurea; R_2 is H or an alkyl group having 1 to 4 carbons and R_3 is H; X is H or a cation.

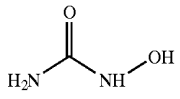
[0476] Other suitable hydroxyureas are disclosed in, e.g., U.S. Pat. No. 4,299,778, wherein R_1 is a phenyl group substituted with one or more fluorine atoms; R_2 is a cyclopropyl group; and R_3 and X is H.

[0477] Other suitable hydroxyureas are disclosed in, e.g., U.S. Pat. No. 5,066,658, wherein R_2 and R_3 together with the adjacent nitrogen form:



[0478] wherein m is 1 or 2, n is 0-2 and Y is an alkyl group.

[0479] In one aspect, the hydroxyurea has the structure:

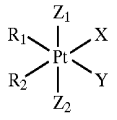


Hydroxyurea

[0480] These compounds are thought to function by inhibiting DNA synthesis.

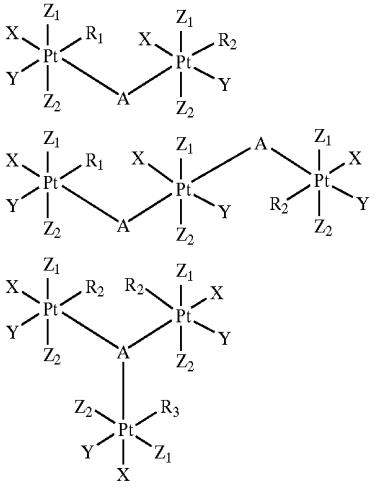
[0481] g) Platinum Complexes

[0482] In another aspect, the therapeutic agent is a platinum compound. In general, suitable platinum complexes may be of Pt(II) or Pt(IV) and have this basic structure:

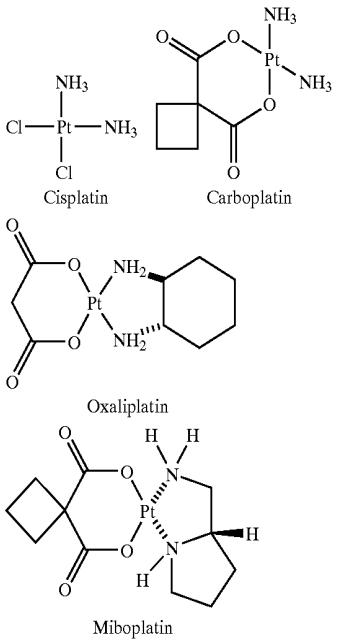


[0483] wherein X and Y are anionic leaving groups such as sulfate, phosphate, carboxylate, and halogen; R_1 and R_2 are alkyl; amine, amino alkyl any may be further substituted, and are basically inert or bridging groups. For Pt(II) complexes Z_1 and Z_2 are non-existent. For Pt(IV) Z_1 and Z_2 may be anionic groups such as halogen, hydroxy, carboxylate, ester, sulfate or phosphate. See, e.g., U.S. Pat. Nos. 4,588,831 and 4,250,189.

[0484] Suitable platinum complexes may contain multiple Pt atoms. See, e.g., U.S. Pat. Nos. 5,409,915 and 5,380,897. For example bisplatinum and triplatinum complexes of the type:



[0485] Exemplary platinum compounds are cisplatin, carboplatin, oxaliplatin, and miboplatin having the structures:



[0486] Other representative platinum compounds include $(CPA)_2Pt[DOLYM]$ and (DACH)Pt[DOLYM] cisplatin (Choi et al., *Arch. Pharmacal Res.* 22(2):151-156, 1999), Cis-$[PtCl_2$(4,7-H-5-methyl-7-oxo]1,2,4[triazolo[1,5-a]pyrimidine)$_2]$ (Navarro et al., *J. Med. Chem.* 41(3):332-338, 1998), [Pt(cis-1,4-DACH)(trans-Cl_2)(CBDCA)].½MeOH cisplatin (Shamsuddin et al., *Inorg. Chem.* 36(25):5969-5971, 1997), 4-pyridoxate diammine hydroxy platinum (Tokunaga et al., *Pharm. Sci.* 3(7):353-356, 1997), Pt(II) . . . Pt(II) $(Pt_2[NHCHN(C(CH_2)(CH_3))]_4)$ (Navarro et al., *Inorg. Chem.* 35(26):7829-7835, 1996), 254-S cisplatin analogue (Koga et al., *Neurol. Res.* 18(3):244-247, 1996), o-phenylenediamine ligand bearing cisplatin analogues (Koeckerbauer & Bednarski, *J. Inorg. Biochem.* 62(4):281-298, 1996), trans, cis-$[Pt(OAc)_2I_2(en)]$ (Kratochwil et al., *J. Med. Chem.* 39(13):2499-2507, 1996), estrogenic 1,2-diarylethylenediamine ligand (with sulfur-containing amino acids and glutathione) bearing cisplatin analogues (Bednarski, *J. Inorg. Biochem.* 62(1):75, 1996), cis-1,4-diaminocyclohexane cisplatin analogues (Shamsuddin et al., *J. Inorg. Biochem.* 61(4):291-301,1996), 5' orientational isomer of cis-[$Pt(NH_3)$(4-aminoTEMP-O){d(GpG)}] (Dunham & Lippard, *J. Am. Chem. Soc.* 117(43):10702-12,1995), chelating diamine-bearing cisplatin analogues (Koeckerbauer& Bednarski, *J. Pharm. Sci.* 84(7):819-23, 1995), 1,2-diarylethyleneamine ligand-bearing cisplatin analogues (Otto et al., *J. Cancer Res. Clin. Oncol.* 121(1):31-8, 1995), (ethylenediamine)platinum(II) complexes (Pasini et al., *J. Chem. Soc., Dalton Trans.* 4:579-85, 1995), CI-973 cisplatin analogue (Yang et al., *Int. J. Oncol.* 5(3):597-602, 1994), cis-diaminedichloroplatinum(II) and its analogues cis-1,1-cyclobutanedicarbosylato(2R)-2-methyl-1,4-butanediamineplatinum(II) and cis-diammine(glycolato)platinum (Claycamp & Zimbrick, *J. Inorg. Biochem.* 26(4):257-67, 1986; Fan et al., *Cancer Res.* 48(11):3135-9, 1988; Heiger-Bemays et al., *Biochemistry* 29(36):8461-6, 1990; Kikkawa et al., *J. Exp. Clin. Cancer Res.* 12(4):233-40, 1993; Murray et al., *Biochemistry* 31(47):11812-17, 1992; Takahashi et al., *Cancer Chemother. Pharmacol.* 33(1):31-5,1993), cis-amine-cyclohexylamine-dichloroplatinum(II) (Yoshida et al., *Biochem. Pharmacol.* 48(4):793-9, 1994), gem-diphosphonate cisplatin analogues (FR 2683529), (meso-1,2-bis(2,6-dichloro-4-hydroxyplenyl)ethylenediamine) dichloroplatinum(II) (Bednarski et al., *J. Med. Chem.* 35(23):4479-85, 1992), cisplatin analogues containing a tethered dansyl group (Hartwig et al., *J. Am. Chem. Soc.* 114(21):8292-3, 1992), platinum(II) polyamines (Siegmann et al., *Inorg. Met.-Containing Polym. Mater.*, (*Proc. Am. Chem. Soc. Int. Symp.*), 335-61, 1990), cis-(3H)dichloro(ethylenediamine-)platinum(II) (Eastman, *Anal. Biochem.* 197(2):311-15, 1991), trans-diamminedichloroplatinum(II) and cis-$(Pt(NH_3)_2(N_3$-cytosine)Cl) (Bellon & Lippard, *Biophys. Chem.* 35(2-3):179-88, 1990), 3H-cis-1,2-diaminocyclohexanedichloroplatinum(II) and 3H-cis-1,2-diaminocyclohexane-malonatoplatinum (II) (Oswald et al., *Res. Commun. Chem. Pathol. Pharmacol.* 64(1):41-58, 1989), diaminocarboxylatoplatinum (EPA 296321), trans-(D,1)-1,2-diaminocyclohexane carrier ligand-bearing platinum analogues (Wyrick & Chaney, *J. Labelled Compd. Radiopharm.* 25(4):349-57, 1988), aminoalkylaminoanthraquinone-derived cisplatin analogues (Kitov et al., *Eur. J. Med. Chem.* 23(4):381-3, 1988), spiroplatin, carboplatin, iproplatin and JM40 platinum analogues (Schroyen et al., *Eur. J. Cancer Clin. Oncol.* 24(8):1309-12, 1988), bidentate tertiary diamine-containing cisplatinum derivatives (Orbell et al., *Inorg. Chim. Acta* 152(2):125-34, 1988), platinum(II), platinum(IV) (Liu & Wang, *Shandong Yike Daxue Xuebao* 24(1):35-41, 1986), cis-diammine(1,1-cyclobutanedicarboxylato-)platinum(II) (carboplatin, JM8) and ethylenediammine-malonatoplatinum(II) (JM40) (Begg et al., *Radiother. Oncol.* 9(2):157-65, 1987), JM8 and JM9 cisplatin analogues (Harstrick et al., *Int. J. Androl.* 10(1); 139-45, 1987), $(NPr4)_2$((PtCL4).cis-PtCl2—$(NH2Me)_2$)) (Brammer et al., *J. Chem. Soc., Chem. Commun.* 6:443-5, 1987), aliphatic tricarboxylic acid platinum complexes (EPA 185225), and cis-dichloro(amino acid)(tert-butylamine-)platinum(II) complexes (Pasini & Bersanetti, *Inorg. Chim.*

Acta 107(4):259-67, 1985). These compounds are thought to function by binding to DNA, i.e., acting as alkylating agents of DNA.

[0487] As medical implants are made in a variety of configurations and sizes, the exact dose administered may vary with device size, surface area, design and portions of the implant coated. However, certain principles can be applied in the application of this art. Drug dose can be calculated as a function of dose per unit area (of the portion of the device being coated), total drug dose administered can be measured and appropriate surface concentrations of active drug can be determined. Regardless of the method of application of the drug to the cardiac implant, the preferred anticancer agents, used alone or in combination, may be administered under the following dosing guidelines:

[0488] (a) Anthracyclines. Utilizing the anthracycline doxorubicin as an example, whether applied as a polymer coating, incorporated into the polymers which make up the implant components, or applied without a carrier polymer, the total dose of doxorubicin applied to the implant should not exceed 25 mg (range of 0.1 μg to 25 mg). In a particularly preferred embodiment, the total amount of drug applied should be in the range of 1 μg to 5 mg. The dose per unit area (i.e., the amount of drug as a function of the surface area of the portion of the implant to which drug is applied and/or incorporated) should fall within the range of 0.01 μg-100 μg per mm^2 of surface area. In a particularly preferred embodiment, doxorubicin should be applied to the implant surface at a dose of 0.1 $\mu g/mm^2$-10 $\mu g/mm^2$. As different polymer and non-polymer coatings may release doxorubicin at differing rates, the above dosing parameters should be utilized in combination with the release rate of the drug from the implant surface such that a minimum concentration of 10^{-8}-10^{-4} M of doxorubicin is maintained on the surface. It is necessary to insure that surface drug concentrations exceed concentrations of doxorubicin known to be lethal to multiple species of bacteria and fungi (i.e., are in excess of 10^{-4} M; although for some embodiments lower concentrations are sufficient). In a preferred embodiment, doxorubicin is released from the surface of the implant such that anti-infective activity is maintained for a period ranging from several hours to several months. In a particularly preferred embodiment the drug is released in effective concentrations for a period ranging from 1 week-6 months. It should be readily evident based upon the discussions provided herein that analogues and derivatives of doxorubicin (as described previously) with similar functional activity can be utilized for the purposes of this invention; the above dosing parameters are then adjusted according to the relative potency of the analogue or derivative as compared to the parent compound (e.g., a compound twice as potent as doxorubicin is administered at half the above parameters, a compound half as potent as doxorubicin is administered at twice the above parameters, etc.).

[0489] Utilizing mitoxantrone as another example of an anthracycline, whether applied as a polymer coating, incorporated into the polymers which make up the implant, or applied without a carrier polymer, the total dose of mitoxantrone applied should not exceed 5 mg (range of 0.01 μg to 5 mg). In a particularly preferred embodiment, the total amount of drug applied should be in the range of 0.1 μg to 3 mg. The dose per unit area (i.e., the amount of drug as a function of the surface area of the portion of the implant to which drug is applied and/or incorporated) should fall within the range of 0.01 μg-20 μg per mm^2 of surface area. In a particularly preferred embodiment, mitoxantrone should be applied to the implant surface at a dose of 0.05 $\mu g/mm^2$-5 $\mu g/mm^2$. As different polymer and non-polymer coatings will release mitoxantrone at differing rates, the above dosing parameters should be utilized in combination with the release rate of the drug from the implant surface such that a minimum concentration of 10^{-4}-10^{-8} M of mitoxantrone is maintained. It is necessary to insure that drug concentrations on the implant surface exceed concentrations of mitoxantrone known to be lethal to multiple species of bacteria and fungi (i.e., are in excess of 10^{-5} M; although for some embodiments lower drug levels will be sufficient). In a preferred embodiment, mitoxantrone is released from the surface of the implant such that anti-infective activity is maintained for a period ranging from several hours to several months. In a particularly preferred embodiment the drug is released in effective concentrations for a period ranging from 1 week-6 months. It should be readily evident based upon the discussions provided herein that analogues and derivatives of mitoxantrone (as described previously) with similar functional activity can be utilized for the purposes of this invention; the above dosing parameters are then adjusted according to the relative potency of the analogue or derivative as compared to the parent compound (e.g., a compound twice as potent as mitoxantrone is administered at half the above parameters, a compound half as potent as mitoxantrone is administered at twice the above parameters, etc.).

[0490] (b) Fluoropyrimidines Utilizing the fluoropyrimidine 5-fluorouracil as an example, whether applied as a polymer coating, incorporated into the polymers which make up the implant, or applied without a carrier polymer, the total dose of 5-fluorouracil applied should not exceed 250 mg (range of 1.0 μg to 250 mg). In a particularly preferred embodiment, the total amount of drug applied should be in the range of 10 μg to 25 mg. The dose per unit area (i.e., the amount of drug as a function of the surface area of the portion of the implant to which drug is applied and/or incorporated) should fall within the range of 0.05 μg-200 μg per mm^2 of surface area. In a particularly preferred embodiment, 5-fluorouracil should be applied to the implant surface at a dose of 0.5 $\mu g/mm^2$-50 $\mu g/mm^2$. As different polymer and non-polymer coatings will release 5-fluorouracil at differing rates, the above dosing parameters should be utilized in combination with the release rate of the drug from the implant surface such that a minimum concentration of 10^{-4}-10^{-7} M of 5-fluorouracil is maintained. It is necessary to insure that surface drug concentrations exceed concentrations of 5-fluorouracil known to be lethal to numerous species of bacteria and fungi (i.e., are in excess of 10^{-4} M; although for some embodiments lower drug levels will be sufficient). In a preferred embodiment, 5-fluorouracil is released from the implant surface such that anti-infective activity is maintained for a period ranging from several hours to several months. In a particularly preferred embodiment the drug is released in effective concentrations for a period ranging from 1 week-6 months. It should be readily evident based upon the discussions provided herein that analogues and derivatives of 5-fluorouracil (as described previously) with similar functional activity can be utilized for the purposes of this invention; the above dosing parameters are then adjusted according to the relative potency of

the analogue or derivative as compared to the parent compound (e.g., a compound twice as potent as 5-fluorouracil is administered at half the above parameters, a compound half as potent as 5-fluorouracil is administered at twice the above parameters, etc.).

[0491] (c) Podophylotoxins Utilizing the podophylotoxin etoposide as an example, whether applied as a polymer coating, incorporated into the polymers which make up the cardiac implant, or applied without a carrier polymer, the total dose of etoposide applied should not exceed 25 mg (range of 0.1 μg to 25 mg). In a particularly preferred embodiment, the total amount of drug applied should be in the range of 1 μg to 5 mg. The dose per unit area (i.e., the amount of drug as a function of the surface area of the portion of the implant to which drug is applied and/or incorporated) should fall within the range of 0.01 μg-100 μg per mm^2 of surface area. In a particularly preferred embodiment, etoposide should be applied to the implant surface at a dose of 0.1 $\mu g/mm^2$-10 $\mu g/mm^2$. As different polymer and non-polymer coatings will release etoposide at differing rates, the above dosing parameters should be utilized in combination with the release rate of the drug from the implant surface such that a concentration of 10^{-4}-10^{-7} M of etoposide is maintained. It is necessary to insure that surface drug concentrations exceed concentrations of etoposide known to be lethal to a variety of bacteria and fungi (i.e., are in excess of 10^{-5} M; although for some embodiments lower drug levels will be sufficient). In a preferred embodiment, etoposide is released from the surface of the implant such that anti-infective activity is maintained for a period ranging from several hours to several months. In a particularly preferred embodiment the drug is released in effective concentrations for a period ranging from 1 week-6 months. It should be readily evident based upon the discussions provided herein that analogues and derivatives of etoposide (as described previously) with similar functional activity can be utilized for the purposes of this invention; the above dosing parameters are then adjusted according to the relative potency of the analogue or derivative as compared to the parent compound (e.g., a compound twice as potent as etoposide is administered at half the above parameters, a compound half as potent as etoposide is administered at twice the above parameters, etc.).

[0492] It may be readily evident based upon the discussions provided herein that combinations of anthracyclines (e.g., doxorubicin or mitoxantrone), fluoropyrimidines (e.g., 5-fluorouracil), folic acid antagonists (e.g., methotrexate and/or podophylotoxins (e.g., etoposide) can be utilized to enhance the antibacterial activity of the composition.

[0493] In another aspect, an anti-infective agent (e.g., anthracyclines (e.g., doxorubicin or mitoxantrone), fluoropyrimidines (e.g., 5-fluorouracil), folic acid antagonists (e.g., methotrexate and/or podophylotoxins (e.g., etoposide)) can be combined with traditional antibiotic and/or antifungal agents to enhance efficacy. The anti-infective agent may be further combined with anti-thrombotic and/or antiplatelet agents (for example, heparin, dextran sulphate, danaparoid, lepirudin, hirudin, AMP, adenosine, 2-chloroadenosine, aspirin, phenylbutazone, indomethacin, meclofenamate, hydrochloroquine, dipyridamole, iloprost, ticlopidine, clopidogrel, abcixamab, eptifibatide, tirofiban, streptokinase, and/or tissue plasminogen activator) to enhance efficacy.

[0494] In addition to incorporation of the above-mentioned therapeutic agents (i.e., anti-infective agents or fibrosis-inhibiting agents), one or more other pharmaceutically active agents can be incorporated into the present compositions and devices to improve or enhance efficacy. Representative examples of additional therapeutically active agents include, by way of example and not limitation, anti-thrombotic agents, anti-proliferative agents, anti-inflammatory agents, neoplastic agents, enzymes, receptor antagonists or agonists, hormones, antibiotics, antimicrobial agents, antibodies, cytokine inhibitors, IMPDH (inosine monophosplate dehydrogenase) inhibitors tyrosine kinase inhibitors, MMP inhibitors, p38 MAP kinase inhibitors, immunosuppressants, apoptosis antagonists, caspase inhibitors, and JNK inhibitors.

[0495] Implantable electrical devices and compositions for use with implantable electrical devices may further include an anti-thrombotic agent and/or antiplatelet agent and/or a thrombolytic agent, which reduces the likelihood of thrombotic events upon implantation of a medical implant. Within various embodiments of the invention, a device is coated on one aspect with a composition which inhibits fibrosis (and/or restenosis), as well as being coated with a composition or compound which prevents thrombosis on another aspect of the device. Representative examples of anti-thrombotic and/or antiplatelet and/or thrombolytic agents include heparin, heparin fragments, organic salts of heparin, heparin complexes (e.g., benzalkonium heparinate, tridodecylammonium heparinate), dextran, sulfonated carbohydrates such as dextran sulphate, coumadin, coumarin, heparinoid, danaparoid, argatroban chitosan sulfate, chondroitin sulfate, danaparoid, lepirudin, hirudin, AMP, adenosine, 2-chloroadenosine, acetylsalicylic acid, phenylbutazone, indomethacin, meclofenamate, hydrochloroquine, dipyridamole, iloprost, streptokinase, factor Xa inhibitors, such as DX9065a, magnesium, and tissue plasminogen activator. Further examples include plasminogen, lys-plasminogen, alpha-2-antiplasmin, urokinase, aminocaproic acid, ticlopidine, clopidogrel, trapidil (triazolopyrimidine), naftidrofuryl, auriritricarboxylic acid and glycoprotein IIb/IIIa inhibitors such as abcixamab, eptifibatide, and tirogiban. Other agents capable of affecting the rate of clotting include glycosaminoglycans, danaparoid, 4-hydroxycourmarin, warfarin sodium, dicumarol, phenprocoumon, indan-1,3-dione, acenocoumarol, anisindione, and rodenticides including bromadiolone, brodifacoum, diphenadione, chlorophacinone, and pidnone.

[0496] Compositions for use with electrical devices may be or include a hydrophilic polymer gel that itself has anti-thrombogenic properties. For example, the composition can be in the form of a coating that can comprise a hydrophilic, biodegradable polymer that is physically removed from the surface of the device over time, thus reducing adhesion of platelets to the device surface. The gel composition can include a polymer or a blend of polymers. Representative examples include alginates, chitosan and chitosan sulfate, hyaluronic acid, dextran sulfate, PLURONIC polymers (e.g., F-127 or F87), chain extended PLURONIC polymers, various polyester-polyether block copolymers of various configurations (e.g., AB, ABA, or BAB, where A is a polyester such as PLA, PGA, PLGA, PCL or the like), examples of which include MePEG-PLA, PLA-PEG-PLA, and the like). In one embodiment, the anti-thrombotic composition can include a crosslinked gel

formed from a combination of molecules (e.g., PEG) having two or more terminal electrophilic groups and two or more nucleophilic groups.

[0497] Electrical devices and compositions for use with implantable electrical devices may further include a compound which acts to have an inhibitory effect on pathological processes in or around the treatment site. In certain aspects, the agent may be selected from one of the following classes of compounds: anti-inflammatory agents (e.g., dexamethasone, cortisone, fludrocortisone, prednisone, prednisolone, 6α-methylprednisolone, triamcinolone, betamethasone, and aspirin); MMP inhibitors (e.g., batimistat, marimistat, TIMP's representative examples of which are included in U.S. Pat. Nos. 5,665,777; 5,985,911; 6,288,261; 5,952,320; 6,441,189; 6,235,786; 6,294,573; 6,294,539; 6,563,002; 6,071,903; 6,358,980; 5,852,213; 6,124,502; 6,160,132; 6,197,791; 6,172,057; 6,288,086; 6,342,508; 6,228,869; 5,977,408; 5,929,097; 6,498,167; 6,534,491; 6,548,524; 5,962,481; 6,197,795; 6,162,814; 6,441,023; 6,444,704; 6,462,073; 6,162,821; 6,444,639; 6,262,080; 6,486,193; 6,329,550; 6,544,980; 6,352,976; 5,968,795; 5,789,434; 5,932,763; 6,500,847; 5,925,637; 6,225,314; 5,804,581; 5,863,915; 5,859,047; 5,861,428; 5,886,043; 6,288,063; 5,939,583; 6,166,082; 5,874,473; 5,886,022; 5,932,577; 5,854,277; 5,886,024; 6,495,565; 6,642,255; 6,495,548; 6,479,502; 5,696,082; 5,700,838; 6,444,639; 6,262,080; 6,486,193; 6,329,550; 6,544,980; 6,352,976; 5,968,795; 5,789,434; 5,932,763; 6,500,847; 5,925,637; 6,225,314; 5,804,581; 5,863,915; 5,859,047; 5,861,428; 5,886,043; 6,288,063; 5,939,583; 6,166,082; 5,874,473; 5,886,022; 5,932,577; 5,854,277; 5,886,024; 6,495,565; 6,642,255; 6,495,548; 6,479,502; 5,696,082; 5,700,838; 5,861,436; 5,691,382; 5,763,621; 5,866,717; 5,902,791; 5,962,529; 6,017,889; 6,022,873; 6,022,898; 6,103,739; 6,127,427; 6,258,851; 6,310,084; 6,358,987; 5,872,152; 5,917,090; 6,124,329; 6,329,373; 6,344,457; 5,698,706; 5,872,146; 5,853,623; 6,624,144; 6,462,042; 5,981,491; 5,955,435; 6,090,840; 6,114,372; 6,566,384; 5,994,293; 6,063,786; 6,469,020; 6,118,001; 6,187,924; 6,310,088; 5,994,312; 6,180,611; 6,110,896; 6,380,253; 5,455,262; 5,470,834; 6,147,114; 6,333,324; 6,489,324; 6,362,183; 6,372,758; 6,448,250; 6,492,367; 6,380,258; 6,583,299; 5,239,078; 5,892,112; 5,773,438; 5,696,147; 6,066,662; 6,600,057; 5,990,158; 5,731,293; 6,277,876; 6,521,606; 6,168,807; 6,506,414; 6,620,813; 5,684,152; 6,451,791; 6,476,027; 6,013,649; 6,503,892; 6,420,427; 6,300,514; 6,403,644; 6,177,466; 6,569,899; 5,594,006; 6,417,229; 5,861,510; 6,156,798; 6,387,931; 6,350,907; 6,090,852; 6,458,822; 6,509,337; 6,147,061; 6,114,568; 6,118,016; 5,804,593; 5,847,153; 5,859,061; 6,194,451; 6,482,827; 6,638,952; 5,677,282; 6,365,630; 6,130,254; 6,455,569; 6,057,369; 6,576,628; 6,110,924; 6,472,396; 6,548,667; 5,618,844; 6,495,578; 6,627,411; 5,514,716; 5,256,657; 5,773,428; 6,037,472; 6,579,890; 5,932,595; 6,013,792; 6,420,415; 5,532,265; 5,639,746; 5,672,598; 5,830,915; 6,630,516; 5,324,634; 6,277,061; 6,140,099; 6,455,570; 5,595,885; 6,093,398; 6,379,667; 5,641,636; 5,698,404; 6,448,058; 6,008,220; 6,265,432; 6,169,103; 6,133,304; 6,541,521; 6,624,196; 6,307,089; 6,239,288; 5,756,545; 6,020,366; 6,117,869; 6,294,674; 6,037,361; 6,399,612; 6,495,568; 6,624,177; 5,948,780; 6,620,835; 6,284,513; 5,977,141; 6,153,612; 6,297,247; 6,559,142; 6,555,535; 6,350,885; 5,627,206; 5,665,764; 5,958,972; 6,420,408; 6,492,422; 6,340,709; 6,022,948; 6,274,703; 6,294,694; 6,531,499; 6,465,508; 6,437,177; 6,376,665; 5,268,384; 5,183,900; 5,189,178; 6,511,993; 6,617,354; 6,331,563; 5,962,466; 5,861,427; 5,830,869; and 6,087,359), cytokine inhibitors (chlorpromazine, mycophenolic acid, rapamycin, 1α-hydroxy vitamin D_3), IMPDH (inosine monophosplate dehydrogenase) inhibitors (e.g., mycophenolic acid, ribaviran, aminothiadiazole, thiophenfurin, tiazofurin, viramidine) (Representative examples are included in U.S. Pat., Nos. 5,536,747; 5,807,876; 5,932,600; 6,054,472; 6,128,582; 6,344,465; 6,395,763; 6,399,773; 6,420,403; 6,479,628; 6,498,178; 6,514,979; 6,518,291; 6,541,496; 6,596,747; 6,617,323; and 6,624,184, U.S. Patent Application Nos. 2002/0040022A1, 2002/0052513A1, 2002/0055483A1, 2002/0068346A1, 2002/0111378A1, 2002/0111495A1, 2002/0123520A1, 2002/0143176A1, 2002/0147160A1, 2002/0161038A1, 2002/0173491A1, 2002/0183315A1, 2002/0193612A1, 2003/0027845A1, 2003/0068302A1, 2003/0105073A1, 2003/0130254A1, 2003/0143197A1, 2003/0144300A1, 2003/0166201A1, 2003/0181497A1, 2003/0186974A1, 2003/0186989A1, and 2003/0195202A1, and PCT Publication Nos. WO 00/24725A1, WO 00/25780A1, WO 00/26197A1, WO 00/51615A1, WO 00/56331A1, WO 00/73288A1, WO 01/00622A1, WO 01/66706A1, WO 01/79246A2, WO 01/81340A2, WO 01/85952A2, WO 02/16382A1, WO 02/18369A2, WO 02/051814A1, WO 02/057287A2, WO 02/057425A2, WO 02/060875A1, WO 02/060896A1, WO 02/060898A1, WO 02/068058A2, WO 03/020298A1, WO 03/037349A1, WO 03/039548A1, WO 03/045901A2, WO 03/047512A2, WO 03/053958A1, WO 03/055447A2, WO 03/059269A2, WO 03/063573A2, WO 03/087071A1, WO 99/001545A1, WO 97/40028A1, WO 97/41211A1, WO 98/40381 A1, and WO 99/55663A1), p38 MAP kinase inhibitors (MAPK) (e.g., GW-2286, CGP-52411, BIRB-798, SB220025, RO-320-1195, RWJ-67657, RWJ-68354, SCIO-469) (Representative examples are included in U.S. Pat. Nos. 6,300,347; 6,316,464; 6,316,466; 6,376,527; 6,444,696; 6,479,507; 6,509,361; 6,579,874, and 6,630,485, and U.S. Patent Application Publication Nos. 2001/0044538A1, 2002/0013354A1, 2002/0049220A1, 2002/0103245A1, 2002/0151491A1, 2002/0156114A1, 2003/0018051A1, 2003/0073832A1, 2003/0130257A1, 2003/0130273A1, 2003/0130319A1, 2003/0139388A1, 2003/0139462A1, 2003/0149031A1, 2003/0166647A1, and 2003/0181411A1, and PCT Publication Nos. WO 00/63204A2, WO 01/21591A1, WO 01/35959A1, WO 01/74811A2, WO 02/18379A2, WO 02/064594A2, WO 02/083622A2, WO 02/094842A2, WO 02/096426A1, WO 02/101015A2, WO 02/103000A2, WO 03/008413A1, WO 03/016248A2, WO 03/020715A1, WO 03/024899A2, WO 03/031431 A1, WO 03/040103A1, WO 03/053940A1, WO 03/053941A2, WO 03/063799A2, WO 03/079986A2, WO 03/080024A2, WO 03/082287A1, WO 97/44467A1, WO 99/01449A1, and WO 99/58523A1), and immunomodulatory agents (rapamycin, everolimus, ABT-578, azathioprine azithromycin, analogues of rapamycin, including tacrolimus and derivatives thereof (e.g., EP 0184162B1 and those described in U.S. Pat. No. 6,258,823) and everolimus and derivatives thereof (e.g., U.S. Pat. No. 5,665,772). Further representative examples of sirolimus analogues and derivatives include ABT-578 and those found in PCT Publication Nos. WO 97/10502, WO 96/41807, WO 96/35423, WO 96/03430, WO 96/00282, WO 95/16691, WO 95/15328, WO 95/07468, WO 95/04738, WO 95/04060, WO 94/25022, WO 94/21644, WO 94/18207, WO

94/10843, WO 94/09010, WO 94/04540, WO 94/02485, WO 94/02137, WO 94/02136, WO 93/25533, WO 93/18043, WO 93/13663, WO 93/11130, WO 93/10122, WO 93/04680, WO 92/14737, and WO 92/05179 and in U.S. Pat. Nos. 6,342,507; 5,985,890; 5,604,234; 5,597,715; 5,583,139; 5,563,172; 5,561,228; 5,561,137; 5,541,193; 5,541,189; 5,534,632; 5,527,907; 5,484,799; 5,457,194; 5,457,182; 5,362,735; 5,324,644; 5,318,895; 5,310,903; 5,310,901; 5,258,389; 5,252,732; 5,247,076; 5,225,403; 5,221,625; 5,210,030; 5,208,241; 5,200,411; 5,198,421; 5,147,877; 5,140,018; 5,116,756; 5,109,112; 5,093,338; and 5,091,389.

[0498] Other examples of biologically active agents which may be combined with implantable electrical devices according to the invention include tyrosine kinase inhibitors, such as imantinib, ZK-222584, CGP-52411, CGP-53716, NVP-MK980-NX, CP-127374, CP-564959, PD-171026, PD-173956, PD-180970, SU-0879, and SKI-606; MMP inhibitors such as nimesulide, PKF-241-466, PKF-242-484, CGS-27023A, SAR-943, primomastat, SC-77964, PNU-171829, AG-3433, PNU-142769, SU-5402, and dexlipotam; p38 MAP kinase inhibitors such as include CGH-2466 and PD-98-59; immunosuppressants such as argyrin B, macrocyclic lactone, ADZ-62-826, CCl-779, tilomisole, amcinonide, FK-778, AVE-1726, and MDL-28842; cytokine inhibitors such as TNF-484A, PD-172084, CP-293121, CP-353164, and PD-168787; NFKB inhibitors, such as, AVE-0547, AVE-0545, and IPL-576092; HMGCoA reductase inhibitors, such as, pravestatin, atorvastatin, fluvastatin, dalvastatin, glenvastatin, pitavastatin, CP-83101, U-20685; apoptosis antagonist (e.g., troloxamine, TCH-346 (N-methyl-N-propargyl-10-aminomethyl-dibenzo(b,f)oxepin); and caspase inhibitors (e.g., PF-5901 (benzenemethanol, alpha-pentyl-3-(2-quinolinylmethoxy)-), and JNK inhibitor (e.g., AS-602801).

[0499] In another aspect, the electrical device may further include an antibiotic (e.g., amoxicillin, trimethoprim-sulfamethoxazole, azithromycin, clarithromycin, amoxicillin-clavulanate, cefprozil, cefuroxime, cefpodoxime, or cefdinir).

[0500] In certain aspects, a polymeric composition comprising a fibrosis-inhibiting agent is combined with an agent that can modify metabolism of the agent in vivo to enhance efficacy of the fibrosis-inhibiting agent. One class of therapeutic agents that can be used to alter drug metabolism includes agents capable of inhibiting oxidation of the anti-scarring agent by cytochrome P450 (CYP). In one embodiment, compositions are provided that include a fibrosis-inhibiting agent (e.g., paclitaxel, rapamycin, everolimus) and a CYP inhibitor, which may be combined (e.g., coated) with any of the devices described herein. Representative examples of CYP inhibitors include flavones, azole antifungals, macrolide antibiotics, HIV protease inhibitors, and anti-sense oligomers. Devices comprising a combination of a fibrosis-inhibiting agent and a CYP inhibitor may be used to treat a variety of proliferative conditions that can lead to undesired scarring of tissue, including intimal hyperplasia, surgical adhesions, and tumor growth.

[0501] Within various embodiments of the invention, a device incorporates or is coated on one aspect, portion or surface with a composition which inhibits fibrosis (and/or restenosis), as well as with a composition or compound which promotes fibrosis on another aspect, portion or surface of the device. Representative examples of agents that promote fibrosis include silk and other irritants (e.g., talc, wool (including animal wool, wood wool, and synthetic wool), talcum powder, copper, metallic beryllium (or its oxides), quartz dust, silica, crystalline silicates), polymers (e.g., polylysine, polyurethanes, poly(ethylene terephthalate), PTFE, poly(alkylcyanoacrylates), and poly(ethylene-co-vinylacetate); vinyl chloride and polymers of vinyl chloride; peptides with high lysine content; growth factors and inflammatory cytokines involved in angiogenesis, fibroblast migration, fibroblast proliferation, ECM synthesis and tissue remodeling, such as epidermal growth factor (EGF) family, transforming growth factor-α (TGF-α), transforming growth factor-β (TGF-β-1, TGF-β-2, TGF-β-3, platelet-derived growth factor (PDGF), fibroblast growth factor (acidic—aFGF; and basic—bFGF), fibroblast stimulating factor-1, activins, vascular endothelial growth factor (including VEGF-2, VEGF-3, VEGF-A, VEGF-B, VEGF-C, placental growth factor—PIGF), angiopoietins, insulin-like growth factors (IGF), hepatocyte growth factor (HGF), connective tissue growth factor (CTGF), myeloid colony-stimulating factors (CSFs), monocyte chemotactic protein, granulocyte-macrophage colony-stimulating factors (GM-CSF), granulocyte colony-stimulating factor (G-CSF), macrophage colony-stimulating factor (M-CSF), erythropoietin, interleukins (particularly IL-1, IL-8, and IL-6), tumor necrosis factor-α (TNFα), nerve growth factor (NGF), interferon-α, interferon-β, histamine, endothelin-1, angiotensin II, growth hormone (GH), and synthetic peptides, analogues or derivatives of these factors are also suitable for release from specific implants and devices to be described later. Other examples include CTGF (connective tissue growth factor); inflammatory microcrystals (e.g., crystalline minerals such as crystalline silicates); bromocriptine, methylsergide, methotrexate, chitosan, N-carboxybutyl chitosan, carbon tetrachloride, thioacetamide, fibrosin, ethanol, bleomycin, naturally occurring or synthetic peptides containing the Arg-Gly-Asp (RGD) sequence, generally at one or both termini (see, e.g., U.S. Pat. No. 5,997,895), and tissue adhesives, such as cyanoacrylate and crosslinked poly(ethylene glycol)—methylated collagen compositions. Other examples of fibrosis-inducing agents include bone morphogenic proteins (e.g., BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 (Vgr-1), BMP-7 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15, and BMP-16. Of these, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, and BMP-7 are of particular utility. Bone morphogenic proteins are described, for example, in U.S. Pat. Nos. 4,877,864; 5,013,649; 5,661,007; 5,688,678; 6,177,406; 6,432,919; and 6,534,268 and Wozney, J. M., et al. (1988) Science: 242(4885); 1528-1534.

[0502] Other representative examples of fibrosis-inducing agents include components of extracellular matrix (e.g., fibronectin, fibrin, fibrinogen, collagen (e.g., bovine collagen), including fibrillar and non-fibrillar collagen, adhesive glycoproteins, proteoglycans (e.g., heparin sulfate, chondroitin sulfate, dermatan sulfate), hyaluronan, secreted protein acidic and rich in cysteine (SPARC), thrombospondins, tenacin, and cell adhesion molecules (including integrins, vitronectin, fibronectin, laminin, hyaluronic acid, elastin, bitronectin), proteins found in basement membranes, and fibrosin) and inhibitors of matrix metalloproteinases, such as TIMPs (tissue inhibitors of matrix metalloproteinases) and synthetic TIMPs, such as, e.g., marimistat, bati-

mistat, doxycycline, tetracycline, minocycline, TROCADE, Ro-1130830, CGS 27023A, and BMS-275291 and analogues and derivatives thereof.

[0503] Although the above therapeutic agents have been provided for the purposes of illustration, it may be understood that the present invention is not so limited. For example, although agents are specifically referred to above, the present invention may be understood to include analogues, derivatives and conjugates of such agents. As an illustration, paclitaxel may be understood to refer to not only the common chemically available form of paclitaxel, but analogues (e.g., TAXOTERE, as noted above) and paclitaxel conjugates (e.g., paclitaxel-PEG, paclitaxel-dextran, or paclitaxel-xylos). In addition, as will be evident to one of skill in the art, although the agents set forth above may be noted within the context of one class, many of the agents listed in fact have multiple biological activities. Further, more than one therapeutic agent may be utilized at a time (i.e., in combination), or delivered sequentially.

[0504] C. Dosages

[0505] Since neurostimulation devices and cardiac rhythm management devices are made in a variety of configurations and sizes, the exact dose administered may vary with device size, surface area and design. However, certain principles can be applied in the application of this art. Drug dose can be calculated as a function of dose (i.e., amount) per unit area of the portion of the device being coated. Surface area can be measured or determined by methods known to one of ordinary skill in the art. Total drug dose administered can be measured and appropriate surface concentrations of active drug can be determined. Drugs are to be used at concentrations that range from several times more than to 10%, 5%, or even less than 1% of the concentration typically used in a single chemotherapeutic systemic dose application. In certain aspects, the drug is released in effective concentrations for a period ranging from 1-90 days. Regardless of the method of application of the drug to the device, the fibrosis-inhibiting agents, used alone or in combination, should be administered under the following dosing guidelines:

[0506] As described above, electrical devices may be used in combination with a composition that includes an anti-scarring agent. The total amount (dose) of anti-scarring agent in or on the device may be in the range of about 0.01 μg-10 μg, or 10 μg-10 mg, or 10 mg-250 mg, or 250 mg-1000 mg, or 1000 mg-2500 mg. The dose (amount) of anti-scarring agent per unit area of device surface to which the agent is applied may be in the range of about 0.01 $\mu g/mm^2$-1 $\mu g/mm^2$, or 1 $\mu g/mm^2$-10 $\mu g/mm^2$, or 10 $\mu g/mm^2$-250 $\mu g/mm^2$, 250 $\mu g/mm^2$-1000 $\mu g/mm^2$, or 1000 $\mu g/mm^2$-2500 $\mu g/mm^2$.

[0507] It should be apparent to one of skill in the art that potentially any anti-scarring agent described above may be utilized alone, or in combination, in the practice of this embodiment.

[0508] In various aspects, the present invention provides a medical device contain an angiogenesis inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a 5-lipoxygenase inhibitor or antagonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a chemokine receptor antagonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a cell cycle inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an anthracycline (e.g., doxorubicin and mitoxantrone) in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a taxane (e.g., paclitaxel or an analogue or derivative of paclitaxel) in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a podophyllotoxin (e.g., etoposide) in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a vinca alkaloid in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a camptothecin or an analogue or derivative thereof in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a platinum compound in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a nitrosourea in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a nitroimidazole in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a folic acid antagonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a cytidine analogue in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a pyrimidine analogue in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a fluoropyrimidine analogue in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a purine analogue in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a nitrogen mustard in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a hydroxyurea in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a mytomicin in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an alkyl sulfonate in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a benzamide in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a nicotinamide in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a halogenated sugar in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a DNA alkylating agent in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an anti-microtubule agent in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a topoisomerase inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a DNA cleaving agent in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an antimetabolite in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an agent that inhibits adenosine deaminase in a dosage as set forth above. In various aspects, the present invention provides a medical

device containing an agent that inhibits purine ring synthesis in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a nucleotide interconversion inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an agent that inhibits dihydrofolate reduction in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an agent that blocks thymidine monophosphate function in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an agent that causes DNA damage in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a DNA intercalation agent in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an agent that is a RNA synthesis inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an agent that is a pyrimidine synthesis inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an agent that inhibits ribonucleotide synthesis in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an agent that inhibits thymidine monophosphate synthesis in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an agent that inhibits DNA synthesis in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an agent that causes DNA adduct formation in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an agent that inhibits protein synthesis in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an agent that inhibits microtubule function in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an immunomodulatory agent (e.g., sirolimus, everolimus, tacrolimus, or an analogue or derivative thereof) in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a heat shock protein 90 antagonist (e.g., geldanamycin) in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an HMG-CoA reductase inhibitor (e.g., simvastatin) in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an inosine monophosphate dehydrogenase inhibitor (e.g., mycophenolic acid, 1-alpha-25 dihydroxy vitamin D_3) in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an NF kappa B inhibitor (e.g., Bay 11-7082) in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an antimycotic agent (e.g., sulconizole) in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a p38 MAP Kinase inhibitor (e.g., SB202190) in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a cyclin dependent protein kinase inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an epidermal growth factor kinase inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an elastase inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a factor Xa inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a farnesyltransferase inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a fibrinogen antagonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a guanylate cyclase stimulant in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a hydroorotate dehydrogenase inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an IKK2 inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an IL-1 antagonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an ICE antagonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an IRAK antagonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an IL-4 agonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a leukotriene inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an MCP-1 antagonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a MMP inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an NO antagonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a phosphodiesterase inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a TGF beta inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a thromboxane A2 antagonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a TNFα antagonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a TACE inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a tyrosine kinase inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a vitronectin inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a fibroblast growth factor inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a protein kinase inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a PDGF receptor kinase inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an endothelial growth factor receptor kinase inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a retinoic acid receptor antagonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a platelet derived growth factor receptor kinase inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a fibrinogen antagonist in

a dosage as set forth above. In various aspects, the present invention provides a medical device containing a bisphosphonate in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a phospholipase A1 inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a histamine H1/H2/H3 receptor antagonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a macrolide antibiotic in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a GPIIb IIIa receptor antagonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an endothelin receptor antagonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a peroxisome proliferator-activated receptor agonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an estrogen receptor agent in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a somastostatin analogue in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a neurokinin 1 antagonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a neurokinin 3 antagonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a VLA-4 antagonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an osteoclast inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a DNA topoisomerase ATP hydrolyzing inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an angiotensin I converting enzyme inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an angiotensin II antagonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an enkephalinase inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a peroxisome proliferator-activated receptor gamma agonist insulin sensitizer in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a protein kinase C inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a ROCK (rho-associated kinase) inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a CXCR3 inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a ltk inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a cytosolic phospholipase A_2-alpha inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a PPAR agonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an Immunosuppressant in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an Erb inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an apoptosis agonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a lipocortin agonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a VCAM-1 antagonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a collagen antagonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing an alpha 2 integrin antagonist in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a TNF alpha inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a nitric oxide inhibitor in a dosage as set forth above. In various aspects, the present invention provides a medical device containing a cathepsin inhibitor in a dosage as set forth above.

[**0509**] Provided below are exemplary dosage ranges for a variety of anti-scarring agents which can be used in conjunction with electrical devices in accordance with the invention. A) Cell cycle inhibitors including doxorubicin and mitoxantrone. Doxorubicin analogues and derivatives thereof: total dose not to exceed 25 mg (range of 0.1 μg to 25 mg); preferred 1 μg to 5 mg. The dose per unit area of 0.01 μg-100 μg per mm^2; preferred dose of 0.1 μg/mm^2-10 μg/mm^2. Minimum concentration of 10^{-8}-10^{-4} M of doxorubicin is to be maintained on the device surface. Mitoxantrone and analogues and derivatives thereof: total dose not to exceed 5 mg (range of 0.01 μg to 5 mg); preferred 0.1 μg to 3 mg. The dose per unit area of the device of 0.01 μg-20 μg per mm^2; preferred dose of 0.05 μg/mm^2-5 μg/mm^2. Minimum concentration of 10^{-8}-10^{-4} M of mitoxantrone is to be maintained on the device surface. B) Cell cycle inhibitors including paclitaxel and analogues and derivatives (e.g., docetaxel) thereof: total dose not to exceed 10 mg (range of 0.1 μg to 10 mg); preferred 1 μg to 3 mg. The dose per unit area of the device of 0.1 μg-10 μg per mm^2; preferred dose of 0.25 μg/mm^2-5 μg/mm^2. Minimum concentration of 10^{-8}-10^{-4} M of paclitaxel is to be maintained on the device surface. (C) Cell cycle inhibitors such as podophyllotoxins (e.g., etoposide): total dose not to exceed 25 mg (range of 0.1 μg to 25 mg); preferred 1 μg to 5 mg. The dose per unit area of the device of 0.01 μg-100 μg per mm^2; preferred dose of 0.1 μg/mm^2-10 μg/mm^2. Minimum concentration of 10^{-8}-10^{-4} M of etoposide is to be maintained on the device surface. (D) Immunomodulators including sirolimus and everolimus. Sirolimus (i.e., Rapamycin, RAPAMUNE): Total dose not to exceed 10 mg (range of 0.1 μg to 10 mg); preferred 10 μg to 1 mg. The dose per unit area of 0.1 μg-100 μg per mm^2; preferred dose of 0.5 μg/mm^2-10 μg/mm^2. Minimum concentration of 10^{-8}-10^{-4} M is to be maintained on the device surface. Everolimus and derivatives and analogues thereof: Total dose should not exceed 10 mg (range of 0.1 μg to 10 mg); preferred 10 μg to 1 mg. The dose per unit area of 0.1 μg-100 μg per mm^2 of surface area; preferred dose of 0.3 μg/mm^2-10 μg/mm^2. Minimum concentration of 10^{-8}-10^{-4} M of everolimus is to be maintained on the device surface. (E) Heat shock protein 90 antagonists (e.g., geldanamycin) and analogues and derivatives thereof: total dose not to exceed 20 mg (range of 0.1 μg to 20 mg); preferred 1 μg to 5 mg. The dose per unit area of the device of 0.1 μg-10 μg per mm^2; preferred dose of 0.25 μg/mm^2-5 μg/mm^2. Minimum concentration of 10^{-8}-10^{-4} M of pacli-

taxel is to be maintained on the device surface. (F) HMG-CoA reductase inhibitors (e.g., simvastatin) and analogues and derivatives thereof: total dose not to exceed 2000 mg (range of 10.0 μg to 2000 mg); preferred 10 μg to 300 mg. The dose per unit area of the device of 1.0 μg-1000 μg per mm^2; preferred dose of 2.5 μg/mm^2-500 μg/mm^2. Minimum concentration of 10^{-8}-10^{-3} M of simvastatin is to be maintained on the device surface. (G) Inosine monophosphate dehydrogenase inhibitors (e.g., mycophenolic acid, 1-alpha-25 dihydroxy vitamin D_3) and analogues and derivatives thereof: total dose not to exceed 2000 mg (range of 10.0 μg to 2000 mg); preferred 10 μg to 300 mg. The dose per unit area of the device of 1.0 μg-1000 μg per mm^2; preferred dose of 2.5 μg/mm^2-500 μg/mm^2. Minimum concentration of 10^{-8}-10^{-3} M of mycophenolic acid is to be maintained on the device surface. (H)NF kappa B inhibitors (e.g., Bay 11-7082) and analogues and derivatives thereof: total dose not to exceed 200 mg (range of 1.0 μg to 200 mg); preferred 1 μg to 50 mg. The dose per unit area of the device of 1.0 μg-100 μg per mm^2; preferred dose of 2.5 μg/mm^2-50 μg/mm^2. Minimum concentration of 10^{-8}-10^{-4} M of Bay 11-7082 is to be maintained on the device surface. (I) Antimycotic agents (e.g., sulconizole) and analogues and derivatives thereof: total dose not to exceed 2000 mg (range of 10.0 μg to 2000 mg); preferred 10 μg to 300 mg. The dose per unit area of the device of 1.0 μg-1000 μg per mm^2; preferred dose of 2.5 μg/mm^2-5001 μg/mm^2. Minimum concentration of 10^{-8}-10^{-3} M of sulconizole is to be maintained on the device surface. (J) p38 MAP kinase inhibitors (e.g., SB202190) and analogues and derivatives thereof: total dose not to exceed 2000 mg (range of 10.0 μg to 2000 mg); preferred 10 μg to 300 mg. The dose per unit area of the device of 1.0 μg-1000 μg per mm^2; preferred dose of 2.5 μg/mm^2-500 μg/mm^2. Minimum concentration of 10^{-8}-10^{-3} M of SB202190 is to be maintained on the device surface. (K) Anti-angiogenic agents (e.g., halofuginone bromide and analogues and derivatives thereof): total dose not to exceed 10 mg (range of 0.1 μg to 10 mg); preferred 1 μg to 3 mg. The dose per unit area of the device of 0.1 μg-10 μg per mm^2; preferred dose of 0.20 μg/mm^2-5 μg/mm^2. Minimum concentration of 10^{-8}-10^{-4} M of halofuginone bromide is to be maintained on the device surface.

[0510] In addition to those described above (e.g., sirolimus, everolimus, and tacrolimus), several other examples of immunomodulators and appropriate dosage ranges for use with neurostimulation and CRM devices include the following: (A) Biolimus and derivatives and analogues thereof: Total dose should not exceed 10 mg (range of 0.1 μg to 10 mg); preferred 10 μg to 1 mg. The dose per unit area of 0.1 μg-100 μg per mm^2 of surface area; preferred dose of 0.3 μg/mm^2-10 μg/mm^2. Minimum concentration of 10^{-8}-10^{-4} M of everolimus is to be maintained on the device surface. (B) Tresperimus and derivatives and analogues thereof: Total dose should not exceed 10 mg (range of 0.1 μg to 10 mg); preferred 10 μg to 1 mg. The dose per unit area of 0.1 μg-100 μg per mm^2 of surface area; preferred dose of 0.3 μg/mm^2-10 μg/mm^2. Minimum concentration of 10^{-8}-10^{-4} M of tresperimus is to be maintained on the device surface. (C) Auranofin and derivatives and analogues thereof: Total dose should not exceed 10 mg (range of 0.1 μg to 10 mg); preferred 10 μg to 1 mg. The dose per unit area of 0.1 μg-100 μg per mm^2 of surface area; preferred dose of 0.3 μg/mm^2-10 μg/mm^2. Minimum concentration of 10^{-8}-10^{-4} M of auranofin is to be maintained on the device surface. (D) 27-O-Demethylrapamycin and derivatives and analogues thereof: Total dose should not exceed 10 mg (range of 0.1 μg to 10 mg); preferred 10 μg to 1 mg. The dose per unit area of 0.1 μg-100 μg per mm^2 of surface area; preferred dose of 0.3 μg/mm^2-10 μg/mm^2. Minimum concentration of 10-810-4 M of 27-O-Demethylrapamycin is to be maintained on the device surface. (E) Gusperimus and derivatives and analogues thereof: Total dose should not exceed 10 mg (range of 0.1 μg to 10 mg); preferred 10 μg to 1 mg. The dose per unit area of 0.1 μg-100 μg per mm^2 of surface area; preferred dose of 0.3 μg/mm^2-10 μg/mm^2. Minimum concentration of 10^{-8}-10^{-4} M of gusperimus is to be maintained on the device surface. (F) Pimecrolimus and derivatives and analogues thereof: Total dose should not exceed 10 mg (range of 0.1 μg to 10 mg); preferred 10 μg to 1 mg. The dose per unit area of 0.1 μg-100 μg per mm^2 of surface area; preferred dose of 0.3 μg/mm^2-10 μg/mm^2. Minimum concentration of 10^{-8}-10^{-4}M of pimecrolimus is to be maintained on the device surface and (G) ABT-578 and analogues and derivatives thereof: Total dose should not exceed 10 mg (range of 0.1 μg to 10 mg); preferred 10 μg to 1 mg. The dose per unit area of 0.1 μg-100 μg per mm^2 of surface area; preferred dose of 0.3 μg/mm^2-10 μg/mm^2. Minimum concentration of 10^{-8}-10^{-4} M of ABT-578 is to be maintained on the device surface.

[0511] In addition to those described above (e.g., paclitaxel, TAXOTERE, and docetaxel), several other examples of anti-microtubule agents and appropriate dosage ranges for use with ear ventilation devices include vinca alkaloids such as vinblastine and vincristine sulfate and analogues and derivatives thereof: total dose not to exceed 10 mg (range of 0.1 μg to 10 mg); preferred 1 μg to 3 mg. Dose per unit area of the device of 0.1 μg-10 μg per mm^2; preferred dose of 0.25 μg/mm^2-5 μg/mm^2. Minimum concentration of 10^{-8}-10^{-4} M of drug is to be maintained on the device surface.

[0512] D. Methods for Generating Medical Devices and Implants which Release a Fibrosis-Inhibiting (or Gliosis-Inhibiting) Agent

[0513] In the practice of this invention, drug-coated or drug-impregnated implants and medical devices are provided which inhibit fibrosis (or gliosis) in and around the device, lead and/or electrode of neurostimulation or cardiac rhythm management (CRM) devices. Within various embodiments, fibrosis (or gliosis) is inhibited by local, regional or systemic release of specific pharmacological agents that become localized to the tissue adjacent to the device or implant. There are numerous neurostimulation and CRM devices where the occurrence of a fibrotic (or gliotic) reaction may adversely affect the functioning of the device or the biological problem for which the device was implanted or used. Typically, fibrotic (or gliotic) encapsulation of the electrical lead (or the growth of fibrous/glial tissue between the lead and the target nerve tissue) slows, impairs, or interrupts electrical transmission of the impulse from the device to the tissue. This can cause the device to function suboptimally or not at all, or can cause excessive drain on battery life as increased energy is required to overcome the electrical resistance imposed by the intervening scar (or glial) tissue. There are numerous methods available for optimizing delivery of the fibrosis-inhibiting (or gliosis-inhibiting) agent to the site of the intervention and several of these are described below.

[0514] 1) Devices and Implants That Release Fibrosis-Inhibiting Agents

[0515] Medical devices or implants of the present invention are coated with, or otherwise adapted to release an agent which inhibits fibrosis (or gliosis) on the surface of, or around, the neurostimulator or CRM device, lead and/or electrode. In one aspect, the present invention provides electrical devices that include an anti-scarring (or anti-gliotic) agent or a composition that includes an anti-scarring (or anti-gliotic) agent such that the overgrowth of granulation (or gliotic) tissue is inhibited or reduced.

[0516] Methods for incorporating fibrosis-inhibiting (or gliosis-inhibiting) compositions onto or into CRM or neurostimulator devices include: (a) directly affixing to the device, lead and/or the electrode a fibrosis-inhibiting (or gliosis-inhibiting) composition (e.g., by either a spraying process or dipping process as described above, with or without a carrier), (b) directly incorporating into the device, lead and/or the electrode a fibrosis-inhibiting (or gliosis-inhibiting) composition (e.g., by either a spraying process or dipping process as described above, with or without a carrier (c) by coating the device, lead and/or the electrode with a substance such as a hydrogel which may in turn absorb the fibrosis-inhibiting (or gliosis-inhibiting) composition, (d) by interweaving fibrosis-inhibiting (or gliosis-inhibiting) composition coated thread (or the polymer itself formed into a thread) into the device, lead and/or electrode structure, (e) by inserting the device, lead and/or the electrode into a sleeve or mesh which is comprised of, or coated with, a fibrosis-inhibiting (or gliosis-inhibiting) composition, (f) constructing the device, lead and/or the electrode itself (or a portion of the device and/or the electrode) with a fibrosis-inhibiting (or gliosis-inhibiting) composition, or (g) by covalently binding the fibrosis-inhibiting (or gliosis-inhibiting) agent directly to the device, lead and/or electrode surface or to a linker (small molecule or polymer) that is coated or attached to the device surface. For these devices, leads and electrodes, the coating process can be performed in such a manner as to: (a) coat the non-electrode portions of the lead or device; (b) coat the electrode portion of the lead; (c) coat the sensor part of the lead; or (d) coat all or parts of the entire device with the fibrosis-inhibiting (or gliosis-inhibiting) composition. In addition to, or alternatively, the fibrosis-inhibiting (or gliosis-inhibiting) agent can be mixed with the materials that are used to make the device, lead and/or electrode such that the fibrosis-inhibiting agent is incorporated into the final product.

[0517] In addition to, or as an alternative to incorporating a fibrosis-inhibiting (or gliosis-inhibiting) agent onto or into the CRM or neurostimulation device, the fibrosis-inhibiting (or gliosis-inhibiting) agent can be applied directly or indirectly to the tissue adjacent to the CRM or neurostimulator device (preferably near the electrode-tissue interface). This can be accomplished by applying the fibrosis-inhibiting (or gliosis inhibiting) agent, with or without a polymeric, non-polymeric, or secondary carrier: (a) to the lead and/or electrode surface (e.g., as an injectable, paste, gel or mesh) during the implantation procedure); (b) to the surface of the tissue (e.g., as an injectable, paste, gel, in situ forming gel or mesh) prior to, immediately prior to, or during, implantation of the CRM or neurostimulation device, lead and/or electrode; (c) to the surface of the lead and/or electrode and/or the tissue surrounding the implanted lead and/or electrode (e.g., as an injectable, paste, gel, in situ forming gel or mesh) immediately after to the implantation of the CRM or neurostimulation device, lead and/or electrode; (d) by topical application of the anti-fibrosis (or gliosis) agent into the anatomical space where the CRM or neurostimulation device, lead and/or electrode may be placed (particularly useful for this embodiment is the use of polymeric carriers which release the fibrosis-inhibiting agent over a period ranging from several hours to several weeks—fluids, suspensions, emulsions, microemulsions, microspheres, pastes, gels, microparticulates, sprays, aerosols, solid implants and other formulations which release the agent can be delivered into the region where the device may be inserted); (e) via percutaneous injection into the tissue surrounding the device, lead and/or electrode as a solution as an infusate or as a sustained release preparation; (f) by any combination of the aforementioned methods. Combination therapies (i.e., combinations of therapeutic agents and combinations with antithrombotic and/or antiplatelet agents) can also be used.

[0518] 2) Systemic, Regional and Local Delivery of Fibrosis-inhibiting (or Gliosis-Inhibiting) Agents

[0519] A variety of drug-delivery technologies are available for systemic, regional and local delivery of therapeutic agents. Several of these techniques may be suitable to achieve preferentially elevated levels of fibrosis-inhibiting (or gliosis-inhibiting) agents in the vicinity of the CRM or neurostimulation device, lead and/or electrode, including: (a) using drug-delivery catheters for local, regional or systemic delivery of fibrosis-inhibiting (or gliosis-inhibiting) agents to the tissue surrounding the device or implant. Typically, drug delivery catheters are advanced through the circulation or inserted directly into tissues under radiological guidance until they reach the desired anatomical location. The fibrosis inhibiting agent can then be released from the catheter lumen in high local concentrations in order to deliver therapeutic doses of the drug to the tissue surrounding the device or implant; (b) drug localization techniques such as magnetic, ultrasonic or MRI-guided drug delivery; (c) chemical modification of the fibrosis-inhibiting (or gliosis-inhibiting) drug or formulation designed to increase uptake of the agent into damaged tissues (e.g., antibodies directed against damaged or healing tissue components such as macrophages, neutrophils, smooth muscle cells, fibroblasts, extracellular matrix components, neovascular tissue); (d) chemical modification of the fibrosis-inhibiting (or gliosis-inhibiting) drug or formulation designed to localize the drug to areas of bleeding or disrupted vasculature; and/or (e) direct injection of the fibrosis-inhibiting (or gliosis-inhibiting) agent, for example, under endoscopic vision.

[0520] 3) Infiltration of Fibrosis-Inhibiting (or Gliosis-Inhibiting) Agents into the Tissue Surrounding a Device or Implant

[0521] Alternatively, the tissue surrounding the CRM or neurostimulation device can be treated with a fibrosis-inhibiting (or gliosis-inhibiting) agent prior to, during, or after the implantation procedure. A fibrosis-inhibiting (or gliosis-inhibiting) agent or a composition comprising a fibrosis-inhibiting (or gliosis-inhibiting) agent may be infiltrated around the device or implant by applying the composition directly and/or indirectly into and/or onto (a) tissue adjacent to the medical device; (b) the vicinity of the

medical device-tissue interface; (c) the region around the medical device; and (d) tissue surrounding the medical device.

[0522] It should be noted that certain polymeric carriers themselves can help prevent the formation of fibrous or gliotic tissue around the CRM or neuroimplant. These carriers are particularly useful for the practice of this embodiment, either alone, or in combination with a fibrosis (or gliosis) inhibiting composition. The following polymeric carriers can be infiltrated (as described in the previous paragraph) into the vicinity of the electrode-tissue interface and include: (a) sprayable collagen-containing formulations such as COSTASIS and CT3, either alone, or loaded with a fibrosis-inhibiting (or gliosis-inhibiting) agent, applied to the implantation site (or the implant/device surface); (b) sprayable PEG-containing formulations such as COSEAL, FOCALSEAL, SPRAYGEL or DURASEAL, either alone, or loaded with a fibrosis-inhibiting (or gliosis-inhibiting) agent, applied to the implantation site (or the implant/device surface); (c) fibrinogen-containing formulations such as FLOSEAL or TISSEAL, either alone, or loaded with a fibrosis-inhibiting (or gliosis-inhibiting) agent, applied to the implantation site (or the implant/device surface); (d) hyaluronic acid-containing formulations such as RESTYLANE, HYLAFORM, PERLANE, SYNVISC, SEPRAFILM, SEPRACOAT, InterGel, LUBRICOAT, loaded with a fibrosis-inhibiting (or gliosis-inhibiting) agent applied to the implantation site (or the implant/device surface); (e) polymeric gels for surgical implantation such as REPEL or FLOWGEL loaded with a fibrosis-inhibiting (or gliosis-inhibiting) agent applied to the implantation site (or the implant/device surface); (f) orthopedic "cements" used to hold prostheses and tissues in place loaded with a fibrosis-inhibiting (or gliosis-inhibiting) agent applied to the implantation site (or the implant/device surface), such as OSTEOBOND (Zimmer), low viscosity cement (LVC) (Wright Medical Technology), SIMPLEX P (Stryker), PALACOS (Smith & Nephew), and ENDURANCE (Johnson & Johnson, Inc.); (g) surgical adhesives containing cyanoacrylates such as DERMABOND, INDERMIL, GLUSTITCH, TISSUMEND, VETBOND, HISTOACRYL BLUE and ORABASE SOOTHE-N-SEAL LIQUID PROTECTANT, either alone, or loaded with a fibrosis-inhibiting (or gliosis-inhibiting) agent, applied to the implantation site (or the implant/device surface); (h) implants containing hydroxyapatite [or synthetic bone material such as calcium sulfate, VITOSS (Orthovita) and CORTOSS (Orthovita)] loaded with a fibrosis-inhibiting (or gliosis-inhibiting) agent applied to the implantation site (or the implant/device surface); (i) other biocompatible tissue fillers loaded with a fibrosis-inhibiting (or gliosis-inhibiting) agent, such as those made by BioCure, 3M Company and Neomend, applied to the implantation site (or the implant/device surface); (j) polysaccharide gels such as the ADCON series of gels either alone, or loaded with a fibrosis-inhibiting (or gliosis-inhibiting) agent, applied to the implantation site (or the implant/device surface); and/or (k) films, sponges or meshes such as INTERCEED, VICRYL mesh, and GELFOAM loaded with a fibrosis-inhibiting (or gliosis-inhibiting) agent applied to the implantation site (or the implant/device surface).

[0523] A preferred polymeric matrix which can be used to help prevent the formation of fibrous or gliotic tissue around the CRM or neuroimplant, either alone or in combination with a fibrosis (or gliosis) inhibiting agent/composition, is formed from reactants comprising either one or both of pentaerythritol poly(ethylene glycol)ether tetra-sulfhydryl] (4-armed thiol PEG, which includes structures having a linking group(s) between a sulfhydryl group(s) and the terminus of the polyethylene glycol backbone) and pentaerythritol poly(ethylene glycol)ether tetra-succinimidyl glutarate] (4-armed NHS PEG, which again includes structures having a linking group(s) between a NHS group(s) and the terminus of the polyethylene glycol backbone) as reactive reagents. Another preferred composition comprises either one or both of pentaerythritol poly(ethylene glycol)ether tetra-amino] (4-armed amino PEG, which includes structures having a linking group(s) between an amino group(s) and the terminus of the polyethylene glycol backbone) and pentaerythritol poly(ethylene glycol)ether tetra-succinimidyl glutarate] (4-armed NHS PEG, which again includes structures having a linking group(s) between a NHS group(s) and the terminus of the polyethylene glycol backbone) as reactive reagents. Chemical structures for these reactants are shown in, e.g., U.S. Pat. No. 5,874,500. Optionally, collagen or a collagen derivative (e.g., methylated collagen) is added to the poly(ethylene glycol)-containing reactant(s) to form a preferred crosslinked matrix that can serve as a polymeric carrier for a therapeutic agent or a stand-alone composition to help prevent the formation of fibrous or gliotic tissue around the CRM or neuroimplant.

[0524] 4) Sustained-Release Preparations of Fibrosis-Inhibiting (or Gliosis-Inhibiting) Agents

[0525] As described previously, desired fibrosis-inhibiting (or gliosis-inhibiting) agents may be admixed with, blended with, conjugated to, or, otherwise modified to contain a polymer composition (which may be either biodegradable or non-biodegradable), or a non-polymeric composition, in order to release the therapeutic agent over a prolonged period of time. For many of the aforementioned embodiments, localized delivery as well as localized sustained delivery of the fibrosis-inhibiting (or gliosis-inhibiting) agent may be required. For example, a desired fibrosis-inhibiting (or gliosis-inhibiting) agent may be admixed with, blended with, conjugated to, or otherwise modified to contain a polymeric composition (which may be either biodegradable or non-biodegradable), or non-polymeric composition, in order to release the fibrosis-inhibiting (or gliosis-inhibiting) agent over a period of time. In certain aspects, the polymer composition may include a bioerodible or biodegradable polymer. Representative examples of biodegradable polymer compositions suitable for the delivery of fibrosis-inhibiting (or gliosis-inhibiting) agents include albumin, collagen, gelatin, hyaluronic acid, starch, cellulose and cellulose derivatives (e.g., methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, cellulose acetate phthalate, cellulose acetate succinate, hydroxypropylmethylcellulose phthalate), casein, dextrans, polysaccharides, fibrinogen, poly(ether ester) multiblock copolymers, based on poly(ethylene glycol) and poly(butylene terephthalate), tyrosine-derived polycarbonates (e.g., U.S. Pat. No. 6,120,491), poly(hydroxyl acids), poly(D,L-lactide), poly(D,L-lactide-co-glycolide), poly(glycolide), poly(hydroxybutyrate), polydioxanone, poly(alkylcarbonate) and poly(orthoesters), degradable polyesters (e.g., polyesters comprising the residues of one or more of the monomers selected from lactide, lactic acid, glycolide, glycolic acid, ϵ-caprolactone, gamma-caprolactone, hydroxyvaleric acid, hydroxybutyric acid, beta-butyrolac-

tone, gamma-butyrolactone, gamma-valerolactone, γ-decanolactone, δ-decanolactone, trimethylene carbonate, 1,4-dioxane-2-one or 1,5-dioxepan-2one.), poly(hydroxyvaleric acid), polydioxanone, poly(ethylene terephthalate), poly(malic acid), poly(tartronic acid), poly(acrylamides), polyanhydrides, polyphosphazenes, poly(amino acids), poly(alkylene oxide)-poly(ester) block copolymers (e.g., X—Y, X—Y—X or Y—X—Y, R—(Y—X)$_n$, R—(X—Y)$_n$ where X is a polyalkylene oxide (e.g., poly(ethylene glycol), methoxy poly(ethylene glycol), poly(propylene glycol), block copolymers of poly(ethylene oxide) and poly(propylene oxide) (e.g., PLURONIC and PLURONIC R polymers) and Y is a polyester (e.g., polyester comprising the residues of one or more of the monomers selected from lactide, lactic acid, glycolide, glycolic acid, e-caprolactone, gamma-caprolactone, hydroxyvaleric acid, hydroxybutyric acid, beta-butyrolactone, gamma-butyrolactone, gamma-valerolactone, γ-decanolactone, δ-decanolactone, trimethylene carbonate, 1,4-dioxane-2-one or 1,5-dioxepan-2one.), R is a multifunctional initiator and copolymers as well as blends thereof)) and their copolymers, branched polymers as well as blends thereof. (see generally, Ilium, L., Davids, S. S. (eds.) "Polymers in Controlled Drug Delivery" Wright, Bristol, 1987; Arshady, J. Controlled Release 17:1-22, 1991; Pitt, *Int. J. Phar.* 59:173-196, 1990; Holland et al., *J. Controlled Release* 4:155-0180, 1986)).

[**0526**] Representative examples of non-degradable polymers suitable for the delivery of fibrosis-inhibiting (or gliosis-inhibiting) agents include poly(ethylene-co-vinyl acetate) ("EVA") copolymers, silicone rubber, acrylic polymers (polyacrylic acid, polymethylacrylic acid, polymethylmethacrylate, poly(butyl methacrylate)), poly(alkylcynoacrylate) (e.g., poly(ethylcyanoacrylate), poly(butylcyanoacrylate) poly(hexylcyanoacrylate) poly(octylcyanoacrylate)), polyethylene, polypropylene, polyamides (nylon 6,6), polyurethanes (e.g., CHRONOFLEX AR and CHRONOFLEX AL (both from CardioTech International, Inc., Woburn, Mass.), BIONATE (Polymer Technology Group, Inc., Emergyville, Calif.), and PELLETHANE (Dow Chemical Company, Midland, Mich.)), poly(ester urethanes), poly(ether urethanes), poly(ester-urea), polyethers (poly(ethylene oxide), poly(propylene oxide), block copolymers based on ethylene oxide and propylene oxide (i.e., copolymers of ethylene oxide and propylene oxide polymers), such as the family of PLURONIC polymers available from BASF Corporation (Mount Olive, N.J.), and poly(tetramethylene glycol)), styrene-based polymers (polystyrene, poly(styrene sulfonic acid), poly(styrene)-block-poly(isobutylene)-block-poly(styrene), poly(styrene)-poly(isoprene) block copolymers), and vinyl polymers (polyvinylpyrrolidone, poly(vinyl alcohol), poly(vinyl acetate phthalate) as well as copolymers and blends thereof. Polymers may also be developed which are either anionic (e.g., alginate, carrageenan, carboxymethyl cellulose, poly(acrylamido-2-methyl propane sulfonic acid) and copolymers thereof, poly(methacrylic acid and copolymers thereof and poly(acrylic acid) and copolymers thereof, as well as blends thereof, or cationic (e.g., chitosan, poly-L-lysine, polyethylenimine, and poly(allyl amine)) and blends thereof (see generally, Dunn et al., *J. Applied Polymer Sci.* 50:353-365, 1993; Cascone et al., *J. Materials Sci.: Materials in Medicine* 5:770-774, 1994; Shiraishi et al., *Biol. Pharm. Bull.* 16(11):1164-1168, 1993; Thacharodi and Rao, *Int'l J. Pharm.* 120:115-118, 1995; Miyazaki et al., *Int'l J. Pharm.* 118:257-263,1995).

[**0527**] Particularly preferred polymeric carriers include poly(ethylene-co-vinyl acetate), polyurethanes (e.g., CHRONOFLEX AR, CHRONOFLEX AL, BIONATE, PELLETHANE), poly (D,L-lactic acid) oligomers and polymers, poly (L-lactic acid) oligomers and polymers, poly (glycolic acid), copolymers of lactic acid and glycolic acid, poly (caprolactone), poly (valerolactone), polyanhydrides, copolymers of poly (caprolactone) or poly (lactic acid) with a polyethylene glycol (e.g., MePEG), silicone rubbers, nitrocellulose, poly(styrene)block-poly(isobutylene)-block-poly(styrene), poly(acrylate) polymers and blends, admixtures, or co-polymers of any of the above. Other preferred polymers include collagen, poly(alkylene oxide)-based polymers, polysaccharides such as hyaluronic acid, chitosan and fucans, and copolymers of polysaccharides with degradable polymers.

[**0528**] Other representative polymers capable of sustained localized delivery of fibrosis-inhibiting (or gliosis-inhibiting) agents include carboxylic polymers, polyacetates, polyacrylamides, polycarbonates, polyethers, polyesters, polyethylenes, polyvinylbutyrals, polysilanes, polyureas, polyurethanes, polyurethanes (e.g., CHRONOFLEX AR, CHRONOFLEX AL, BIONATE, AND PELLETHANE), polyoxides, polystyrenes, polysulfides, polysulfones, polysulfonides, polyvinylhalides, pyrrolidones, rubbers, thermal-setting polymers, cross-linkable acrylic and methacrylic polymers, ethylene acrylic acid copolymers, styrene acrylic copolymers, vinyl acetate polymers and copolymers, vinyl acetal polymers and copolymers, epoxy, melamine, other amino resins, phenolic polymers, and copolymers thereof, water-insoluble cellulose ester polymers (including cellulose acetate propionate, cellulose acetate, cellulose acetate butyrate, cellulose nitrate, cellulose acetate phthalate, and mixtures thereof), polyvinylpyrrolidone, polyethylene glycols, polyethylene oxide, polyvinyl alcohol, polyethers, polysaccharides, hydrophilic polyurethane, polyhydroxyacrylate, dextran, xanthan, hydroxypropyl cellulose, methyl cellulose, and homopolymers and copolymers of N-vinylpyrrolidone, N-vinyllactam, N-vinyl butyrolactam, N-vinyl caprolactam, other vinyl compounds having polar pendant groups, acrylate and methacrylate having hydrophilic esterifying groups, hydroxyacrylate, and acrylic acid, and combinations thereof; cellulose esters and ethers, ethyl cellulose, hydroxyethyl cellulose, cellulose nitrate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, polyurethane, polyacrylate, natural and synthetic elastomers, rubber, acetal, nylon, polyester, styrene polybutadiene, acrylic resin, polyvinylidene chloride, polycarbonate, homopolymers and copolymers of vinyl compounds, polyvinylchloride, polyvinylchloride acetate.

[**0529**] In one embodiment, all or a portion of the device is coated with a primer (bonding) layer and a drug release layer, as described in U.S. patent application entitled, "Stent with Medicated Multi-Layer Hybrid Polymer Coating," filed Sep. 16, 2003 (U.S. Ser. No. 10/662,877).

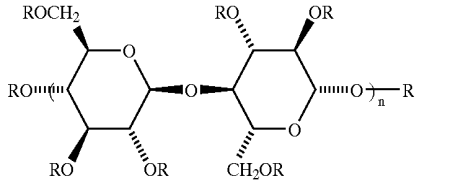
[**0530**] In order to develop a hybrid polymer delivery system for targeted therapy, it is desirable to be able to control and manipulate the properties of the system both in terms of physical and drug release characteristics. The active

agents can be imbibed into a surface hybrid polymer layer, or incorporated directly into the hybrid polymer coating solutions. Imbibing drugs into surface polymer layers is an efficient method for evaluating polymer-drug performance in the laboratory, but for commercial production it may be preferred for the polymer and drug to be premixed in the casting mixture. Greater efficacy can be achieved by combining the two elements in the coating mixtures in order to control the ratio of active agent to polymer in the coatings. Such ratios are important parameters to the final properties of the medicated layers, i.e., they allow for better control of active agent concentration and duration of pharmacological activity.

[0531] Typical polymers used in the drug-release system can include water-insoluble cellulose esters, various polyurethane polymers including hydrophilic and hydrophobic versions, hydrophilic polymers such as polyethylene glycol (PEG), polyethylene oxide (PEO), polyvinylpyrrolidone (PVP), PVP copolymers such as vinyl acetate, hydroxyethyl methacrylate (HEMA) and copolymers such as methylmethacrylate (PMMA-HEMA), and other hydrophilic and hydrophobic acrylate polymers and copolymers containing functional groups such as carboxyl and/or hydroxyl.

[0532] Cellulose esters such as cellulose acetate, cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, and cellulose nitrate may be used. In one aspect of the invention, the therapeutic agent is formulated with a cellulose ester. Cellulose nitrate is a preferred cellulose ester because of its compatibility with the active agents and its ability to impart non-tackiness and cohesiveness to the coatings. Cellulose nitrate has been shown to stabilize entrapped drugs in ambient and processing conditions. Various grades of cellulose nitrate are available and may be used in a coating on a electrical device, including cellulose nitrate having a nitrogen content=11.8-12.2%. Various viscosity grades, including 3.5, 0.5 or 0.25 seconds, may be used in order to provide proper rheological properties when combined with the coating solids used in these formulations. Higher or lower viscosity grades can be used. However, the higher viscosity grades can be more difficult to use because of their higher viscosities. Thus, the lower viscosity grades, such as 3.5, 0.5 or 0.25 seconds, are generally preferred. Physical properties such as tensile strength, elongation, flexibility, and softening point are related to viscosity (molecular weight) and can decrease with the lower molecular weight species, especially below the 0.25 second grades.

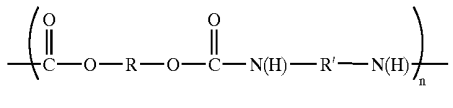
[0533] The cellulose derivatives comprise hydroglucose structures. Cellulose nitrate is a hydrophobic, water-insoluble polymer, and has high water resistance properties. This structure leads to high compatibility with many active agents, accounting for the high degree of stabilization provided to drugs entrapped in cellulose nitrate. The structure of nitrocellulose is given below:



nitrocellulose

[0534] Cellulose nitrate is a hard, relatively inflexible polymer, and has limited adhesion to many polymers that are typically used to make medical devices. Also, control of drug elution dynamics is limited if only one polymer is used in the binding matrix. Accordingly, in one embodiment of the invention, the therapeutic agent is formulated with two or more polymers before being associated with the electrical device. In one aspect, the agent is formulated with both polyurethane ((e.g., CHRONOFLEX AR, CHRONOFLEX AL, BIONATE, and PELLETHANE) and cellulose nitrate to provide a hybrid polymer drug loaded matrix. Polyurethanes provide the hybrid polymer matrix with greater flexibility and adhesion to the electrical device, particularly when the connector has been pre-coated with a primer. Polyurethanes can also be used to slow or hasten the drug elution from coatings. Aliphatic, aromatic, polytetramethylene ether glycol, and polycarbonate are among the types of polyurethanes, which can be used in the coatings. In one aspect, an anti-scarring agent (e.g., paclitaxel) may be incorporated into a carrier that includes a polyurethane and a cellulose derivative. A heparin complex, such as benzalkonium heparinate or tridodecylammonium heparinate), may optionally be included in the formulation.

[0535] From the structure below, it is possible to see how more or less hydrophilic polyurethane polymers may be created based on the number of hydrophilic groups contained in the polymer structures. In one aspect of the invention, the electrical device is associated with a formulation that includes therapeutic agent, cellulose ester, and a polyurethane that is water-insoluble, flexible, and compatible with the cellulose ester.

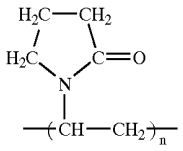


polyurethanes

R = polyether or polyester
R′ = aliphatic or aromatic

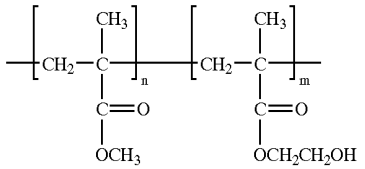
[0536] Polyvinylpyrrolidone (PVP) is a polyamide that possesses unusual complexing and colloidal properties and is essentially physiologically inert. PVP and other hydrophilic polymers are typically biocompatible. PVP may be

incorporated into drug loaded hybrid polymer compositions in order to increase drug release rates. In one embodiment, the concentration of PVP that is used in drug loaded hybrid polymer compositions can be less than 20%. This concentration can not make the layers bioerodable or lubricious. In general, PVP concentrations from <1% to greater than 80% are deemed workable. In one aspect of the invention, the therapeutic agent that is associated with a electrical device is formulated with a PVP polymer.



polyvinylpyrrolidone

[0537] Acrylate polymers and copolymers including polymethylmethacrylate (PMMA) and polymethylmethacrylate hydroxyethyl methacrylate (PMMA/HEMA) are known for their biocompatibility as a result of their widespread use in contact and intraocular lens applications. This class of polymer generally provokes very little smooth muscle and endothelial cell growth, and very low inflammatory response (Bar). These polymers/copolymers are compatible with drugs and the other polymers and layers of the instant invention. Thus, in one aspect, the device is associated with a composition that comprises a anti-scarring agent as described above, and an acrylate polymer or copolymer.



Methylmethacrylate hydroxyethylmethacrylate copolymer

[0538] Representative examples of patents relating to drug-delivery polymers and their preparation include PCT Publication Nos. WO 98/19713, WO 01/17575, WO 01/41821, WO 01/41822, and WO 01/15526 (as well as their corresponding U.S. applications), and U.S. Pat. Nos. 4,500,676, 4,582,865, 4,629,623, 4,636,524, 4,713,448, 4,795,741, 4,913,743, 5,069,899, 5,099,013, 5,128,326, 5,143,724, 5,153,174, 5,246,698, 5,266,563, 5,399,351, 5,525,348, 5,800,412, 5,837,226, 5,942,555, 5,997,517, 6,007,833, 6,071,447, 6,090,995, 6,106,473, 6,110,483, 6,121,027, 6,156,345, 6,214,901, 6,368,611 6,630,155, 6,528,080, RE37,950, 6,46,1631,6,143,314, 5,990,194, 5,792,469, 5,780,044, 5,759,563, 5,744,153, 5,739,176, 5,733,950, 5,681,873, 5,599,552, 5,340,849, 5,278,202, 5,278,201, 6,589,549, 6,287,588, 6,201,072, 6,117,949, 6,004,573, 5,702,717, 6,413,539, and 5,714,159, 5,612,052 and U.S. Patent Application Publication Nos. 2003/0068377, 2002/0192286, 2002/0076441, and 2002/0090398.

[0539] It should be obvious to one of skill in the art that the polymers as described herein can also be blended or copolymerized in various compositions as required to deliver therapeutic doses of fibrosis-inhibiting (or gliosis-inhibiting) agents.

[0540] Polymeric carriers for fibrosis-inhibiting (or gliosis-inhibiting) agents can be fashioned in a variety of forms, with desired release characteristics and/or with specific properties depending upon the device, composition or implant being utilized. For example, polymeric carriers may be fashioned to release a fibrosis-inhibiting (or gliosis-inhibiting) agent upon exposure to a specific triggering event such as pH (see, e.g., Heller et al., "Chemically Self-Regulated Drug Delivery Systems," in *Polymers in Medicine III*, Elsevier Science Publishers B.V., Amsterdam, 1988, pp. 175-188; Kang et al., *J. Applied Polymer Sci.* 48:343-354, 1993; Dong et al., *J. Controlled Release* 19:171-178, 1992; Dong and Hoffman, J. Controlled Release 15:141-152,1991; Kim et al., *J. Controlled Release* 28:143-152, 1994; Cornejo-Bravo et al., *J. Controlled Release* 33:223-229,1995; Wu and Lee, *Pharm. Res.* 10(10):1544-1547, 1993; Serres et al., *Pharm. Res.* 13(2):196-201, 1996; Peppas, "Fundamentals of pH- and Temperature-Sensitive Delivery Systems," in Gumy et al. (eds.), *Pulsatile Drug Delivery*, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 1993, pp. 41-55; Doelker, "Cellulose Derivatives," 1993, in Peppas and Langer (eds.), *Biopolymers I*, Springer-Verlag, Berlin). Representative examples of pH-sensitive polymers include poly(acrylic acid) and its derivatives (including for example, homopolymers such as poly(aminocarboxylic acid); poly(acrylic acid); poly(methyl acrylic acid), copolymers of such homopolymers, and copolymers of poly(acrylic acid) and/or acrylate or acrylamide lmonomers such as those discussed above. Other pH sensitive polymers include polysaccharides such as cellulose acetate phthalate; hydroxypropylmethylcellulose phthalate; hydroxypropylmethylcellulose acetate succinate; cellulose acetate trimellilate; and chitosan. Yet other pH sensitive polymers include any mixture of a pH sensitive polymer and a water-soluble polymer.

[0541] Likewise, fibrosis-inhibiting (or gliosis-inhibiting) agents can be delivered via polymeric carriers which are temperature sensitive (see, e.g., Chen et al., "Novel Hydrogels of a Temperature-Sensitive PLURONIC Grafted to a Bioadhesive Polyacrylic Acid Backbone for Vaginal Drug Delivery," in *Proceed. Intern. Symp. Control. Rel. Bioact. Mater.* 22:167-168, Controlled Release Society, Inc., 1995; Okano, "Molecular Design of Stimuli-Responsive Hydrogels for Temporal Controlled Drug Delivery," in *Proceed. Intern. Symp. Control. Rel. Bioact. Mater.* 22:111-112, Controlled Release Society, Inc., 1995; Johnston et al., *Pharm. Res.* 9(3):425-433,1992; Tung, *Int'l J. Pharm.* 107:85-90, 1994; Harsh and Gehrke, *J. Controlled Release* 17:175-186, 1991; Bae et al., *Pharm. Res.* 8(4):531-537, 1991; Dinarvand and D'Emanuele, *J. Controlled Release* 36:221-227, 1995; Yu and Grainger, "Novel Thermo-sensitive Amphiphilic Gels: Poly N-isopropylacrylamide-co-sodium acrylate-co-n-N-alkylacrylamide Network Synthesis and Physicochemical Characterization," Dept. of Chemical & Biological Sci., Oregon Graduate Institute of Science & Technology, Beaverton, Oreg., pp. 820-821; Zhou and Smid, "Physical Hydrogels of Associative Star Polymers," Polymer Research Institute, Dept. of Chemistry, College of Environmental Science and Forestry, State Univ. of New York, Syracuse, N.Y., pp. 822-823; Hoffman et al., "Characterizing Pore Sizes and Water 'Structure' in Stimuli-

Responsive Hydrogels," Center for Bioengineering, Univ. of Washington, Seattle, Wash., p. 828; Yu and Grainger, "Thermo-sensitive Swelling Behavior in Crosslinked N-isopropylacrylamide Networks: Cationic, Anionic and Ampholytic Hydrogels," Dept. of Chemical & Biological Sci., Oregon Graduate Institute of Science & Technology, Beaverton, Oreg., pp. 829-830; Kim et al., *Pharm. Res.* 9(3):283-290, 1992; Bae et al., *Pharm. Res.* 8(5):624-628, 1991; Kono et al., *J. Controlled Release* 30:69-75, 1994; Yoshida et al., *J. Controlled Release* 32:97-102, 1994; Okano et al., *J. Controlled Release* 36:125-133, 1995; Chun and Kim, J. Controlled Release 38:39-47,1996; D'Emanuele and Dinarvand, *Int'l J. Pharm.* 118:237-242, 1995; Katono et al., *J. Controlled Release* 16:215-228,1991; Hoffman, "Thermally Reversible Hydrogels Containing Biologically Active Species," in Migliaresi et al. (eds.), *Polymers in Medicine III*, Elsevier Science Publishers B.V., Amsterdam, 1988, pp. 161-167; Hoffman, "Applications of Thermally Reversible Polymers and Hydrogels in Therapeutics and Diagnostics," in *Third International Symposium on Recent Advances in Drug Delivery Systems*, Salt Lake City, Utah, Feb. 24-27, 1987, pp. 297-305; Gutowska et al., *J. Controlled Release* 22:95-104, 1992; Palasis and Gehrke, J. Controlled Release 18:1-12, 1992; Paavola et al., *Pharm. Res.* 12(12):1997-2002, 1995).

[0542] Representative examples of thermogelling polymers, and their gelatin temperature (LCST (° C.)) include homopolymers such as poly(N-methyl-N-n-propylacrylamide), 19.8; poly(N-n-propylacrylamide), 21.5; poly(N-methyl-N-isopropylacrylamide), 22.3; poly(N-n-propylmethacrylamide), 28.0; poly(N-isopropylacrylamide), 30.9; poly(N, n-diethylacrylamide), 32.0; poly(N-isopropylmethacrylamide), 44.0; poly(N-cyclopropylacrylamide), 45.5; poly(N-ethylmethyacrylamide), 50.0; poly(N-methyl-N-ethylacrylamide), 56.0; poly(N-cyclopropylmethacrylamide), 59.0; poly(N-ethylacrylamide), 72.0. Moreover thermogelling polymers may be made by preparing copolymers between (among) monomers of the above, or by combining such homopolymers with other water-soluble polymers such as acrylmonomers (e.g., acrylic acid and derivatives thereof, such as methylacrylic acid, acrylate monomers and derivatives thereof, such as butyl methacrylate, butyl acrylate, lauryl acrylate, and acrylamide monomers and derivatives thereof, such as N-butyl acrylamide and acrylamide).

[0543] Other representative examples of thermogelling polymers include cellulose ether derivatives such as hydroxypropyl cellulose, 41° C.; methyl cellulose, 55° C.; hydroxypropylmethyl cellulose, 66° C.; and ethylhydroxyethyl cellulose, polyalkylene oxide-polyester block copolymers of the structure X—Y, Y—X—Y and X—Y—X where X in a polyalkylene oxide and Y is a biodegradable polyester (e.g., PLG-PEG-PLG) and PLURONICs such as F-127, 10-15° C.; L-122, 19° C.; L-92, 26° C.; L-81, 20° C.; and L-61, 24° C.

[0544] Representative examples of patents relating to thermally gelling polymers and their preparation include U.S. Pat. Nos. 6,451,346; 6,201,072; 6,117,949; 6,004,573; 5,702,717; and 5,484,610 and PCT Publication Nos. WO 99/07343; WO 99/18142; WO 03/17972; WO 01/82970; WO 00/18821; WO 97/15287; WO 01/41735; WO 00/00222 and WO 00/38651.

[0545] Fibrosis-inhibiting (or gliosis-inhibiting) agents may be linked by occlusion in the matrices of the polymer, bound by covalent linkages, or encapsulated in microcapsules. Within certain embodiments of the invention, therapeutic compositions are provided in non-capsular formulations such as microspheres (ranging from nanometers to micrometers in size), pastes, threads of various size, films and sprays.

[0546] Within certain aspects of the present invention, therapeutic compositions may be fashioned into particles having any size ranging from 50 nm to 500 μm, depending upon the particular use. These compositions can be in the form of microspheres, microparticles and/or nanoparticles. These compositions can be formed by spray-drying methods, milling methods, coacervation methods, W/O emulsion methods, W/O/W emulsion methods, and solvent evaporation methods. In another embodiment, these compositions can include microemulsions, emulsions, liposomes and micelles. Alternatively, such compositions may also be readily applied as a "spray", which solidifies into a film or coating for use as a device/implant surface coating or to line the tissues of the implantation site. Such sprays may be prepared from microspheres of a wide array of sizes, including for example, from 0.1 μm to 3 μm, from 10 μm to 30 μm, and from 30 μm to 100 μm.

[0547] Therapeutic compositions of the present invention may also be prepared in a variety of paste or gel forms. For example, within one embodiment of the invention, therapeutic compositions are provided which are liquid at one temperature (e.g., temperature greater than 37° C., such as 40° C., 45° C., 50° C., 55° C. or 60° C.), and solid or semi-solid at another temperature (e.g., ambient body temperature, or any temperature lower than 37° C.). Such "thermopastes" may be readily made utilizing a variety of techniques (see, e.g., PCT Publication WO 98/24427). Other pastes may be applied as a liquid, which solidify in vivo due to dissolution of a water-soluble component of the paste and precipitation of encapsulated drug into the aqueous body environment. These "pastes" and "gels" containing fibrosis-inhibiting agents are particularly useful for application to the surface of tissues that will be in contact with the implant or device.

[0548] Within yet other aspects of the invention, the therapeutic compositions of the present invention may be formed as a film or tube. These films or tubes can be porous or non-porous. Such films or tubes are generally less than 5, 4, 3, 2, or 1 mm thick, or less than 0.75 mm, or less than 0.5 mm, or less than 0.25 mm, or, less than 0.10 mm thick. Films or tubes can also be generated of thicknesses less than 50 μm, 25 μm or 10 μm. Such films may be flexible with a good tensile strength (e.g., greater than 50, or greater than 100, or greater than 150 or 200 N/cm^2), good adhesive properties (i.e., adheres to moist or wet surfaces), and have controlled permeability. Fibrosis-inhibiting agents contained in polymeric films are particularly useful for application to the surface of a device or implant as well as to the surface of tissue, cavity or an organ.

[0549] Within further aspects of the present invention, polymeric carriers are provided which are adapted to contain and release a hydrophobic fibrosis-inhibiting (or gliosis-inhibiting) compound, and/or the carrier containing the hydrophobic compound in combination with a carbohydrate, protein or polypeptide. Within certain embodiments, the polymeric carrier contains or comprises regions, pockets, or

granules of one or more hydrophobic compounds. For example, within one embodiment of the invention, hydrophobic compounds may be incorporated within a matrix which contains the hydrophobic fibrosis-inhibiting (or gliosis-inhibiting) compound, followed by incorporation of the matrix within the polymeric carrier. A variety of matrices can be utilized in this regard, including for example, carbohydrates and polysaccharides such as starch, cellulose, dextran, methylcellulose, sodium alginate, heparin, chitosan, hyaluronic acid, proteins or polypeptides such as albumin, collagen and gelatin. Within alternative embodiments, hydrophobic compounds may be contained within a hydrophobic core, and this core contained within a hydrophilic shell.

[0550] Other carriers that may likewise be utilized to contain and deliver fibrosis-inhibiting (or gliosis-inhibiting) agents described herein include: hydroxypropyl cyclodextrin (Cserhati and Hollo, *Int. J. Pharm.* 108:69-75,1994), liposomes (see, e.g., Sharma et al., *Cancer Res.* 53:5877-5881,1993; Sharma and Straubinger, *Pharm. Res.* 11(60):889-896,1994; WO 93/18751; U.S. Pat. No. 5,242,073), liposome/gel (WO 94/26254), nanocapsules (Bartoli et al., *J. Microencapsulation* 7(2):191-197,1990), micelles (Alkan-Onyuksel et al., *Pharm. Res.* 11(2):206-212, 1994), implants (Jampel et al., *Invest. Ophthalm. Vis. Science* 34(11):3076-3083, 1993; Walter et al., *Cancer Res.* 54:22017-2212, 1994), nanoparticles (Violante and Lanzafame PAACR), nanoparticles—modified (U.S. Pat. No. 5,145,684), nanoparticles (surface modified) (U.S. Pat. No. 5,399,363), micelle (surfactant) (U.S. Pat. No. 5,403,858), synthetic phospholipid compounds (U.S. Pat. No. 4,534,899), gas borne dispersion (U.S. Pat. No. 5,301,664), liquid emulsions, foam, spray, gel, lotion, cream, ointment, dispersed vesicles, particles or droplets solid- or liquid-aerosols, microemulsions (U.S. Pat. No. 5,330,756), polymeric shell (nano- and micro-capsule) (U.S. Pat. No. 5,439,686), emulsion (Tarr et al., *Pharm Res.* 4: 62-165, 1987), nanospheres (Hagan et al., *Proc. Intern. Symp. Control Rel. Bioact. Mater.* 22, 1995; Kwon et al., *Pharm Res.* 12(2):192-195; Kwon et al., *Pharm Res.* 10(7):970-974; Yokoyama et al., *J. Contr. Rel.* 32:269-277, 1994; Gref et al., *Science* 263:1600-1603, 1994; Bazile et al., *J. Pharm. Sci.* 84:493-498, 1994) and implants (U.S. Pat. No. 4,882,168).

[0551] Within another aspect of the present invention, polymeric carriers can be materials that are formed in situ. In one embodiment, the precursors can be monomers or macromers that contain unsaturated groups that can be polymerized and/or cross-linked. The monomers or macromers can then, for example, be injected into the treatment area or onto the surface of the treatment area and polymerized in situ using a radiation source (e.g., visible light, UV light) or a free radical system (e.g., potassium persulfate and ascorbic acid or iron and hydrogen peroxide). The polymerization step can be performed immediately prior to, simultaneously to or post injection of the reagents into the treatment site. Representative examples of compositions that undergo free radical polymerization reactions are described in WO 01/44307, WO 01/68720, WO 02/072166, WO 03/043552, WO 93/17669, WO 00/64977, U.S. Pat. Nos. 5,900,245, 6,051,248, 6,083,524, 6,177,095, 6,201,065, 6,217,894, 6,639,014, 6,352,710, 6,410,645, 6,531,147, 5,567,435, 5,986,043, 6,602,975, and U.S. Patent Application Publication Nos. 2002/012796A1, 2002/0127266A1, 2002/0151650A1, 2003/0104032A1, 2002/0091229A1, and 2003/0059906A1.

[0552] As mentioned elsewhere herein, the present invention provides for polymeric crosslinked matrices, and polymeric carriers, that may be used to assist in the prevention of the formation or growth of fibrous connective tissue or glial tissue. The composition may contain and deliver fibrosis-inhibiting (or gliosis-inhibiting) agents in the vicinity of the medical device. The following compositions are particularly useful when it is desired to infiltrate around the device, with or without a fibrosis-inhibiting agent. Such polymeric materials may be prepared from, e.g., (a) synthetic materials, (b) naturally-occurring materials, or (c) mixtures of synthetic and naturally occurring materials. The matrix may be prepared from, e.g., (a) a one-component, i.e., self-reactive, compound, or (b) two or more compounds that are reactive with one another. Typically, these materials are fluid prior to delivery, and thus can be sprayed or otherwise extruded from a device in order to deliver the composition. After delivery, the component materials react with each other, and/or with the body, to provide the desired affect. In some instances, materials that are reactive with one another must be kept separated prior to delivery to the patient, and are mixed together just prior to being delivered to the patient, in order that they maintain a fluid form prior to delivery. In a preferred aspect of the invention, the components of the matrix are delivered in a liquid state to the desired site in the body, whereupon in situ polymerization occurs.

[0553] First and Second Synthetic Polymers

[0554] In one embodiment, crosslinked polymer compositions (in other words, crosslinked matrices) are prepared by reacting a first synthetic polymer containing two or more nucleophilic groups with a second synthetic polymer containing two or more electrophilic groups, where the electrophilic groups are capable of covalently binding with the nucleophilic groups. In one embodiment, the first and second polymers are each non-immunogenic. In another embodiment, the matrices are not susceptible to enzymatic cleavage by, e.g., a matrix metalloproteinase (e.g., collagenase) and are therefore expected to have greater long-term persistence in vivo than collagen-based compositions.

[0555] As used herein, the term "polymer" refers inter alia to polyalkyls, polyamino acids, polyalkyleneoxides and polysaccharides. Additionally, for external or oral use, the polymer may be polyacrylic acid or carbopol. As used herein, the term "synthetic polymer" refers to polymers that are not naturally occurring and that are produced via chemical synthesis. As such, naturally occurring proteins such as collagen and naturally occurring polysaccharides such as hyaluronic acid are specifically excluded. Synthetic collagen, and synthetic hyaluronic acid, and their derivatives, are included. Synthetic polymers containing either nucleophilic or electrophilic groups are also referred to herein as "multifunctionally activated synthetic polymers." The term "multifunctionally activated" (or, simply, "activated") refers to synthetic polymers which have, or have been chemically modified to have, two or more nucleophilic or electrophilic groups which are capable of reacting with one another (i.e., the nucleophilic groups react with the electrophilic groups) to form covalent bonds. Types of multifunctionally activated synthetic polymers include difunctionally activated, tetrafunctionally activated, and star-branched polymers.

[0556] Multifunctionally activated synthetic polymers for use in the present invention must contain at least two, more preferably, at least three, functional groups in order to form a three-dimensional crosslinked network with synthetic polymers containing multiple nucleophilic groups (i.e., "multi-nucleophilic polymers"). In other words, they must be at least difunctionally activated, and are more preferably trifunctionally or tetrafunctionally activated. If the first synthetic polymer is a difunctionally activated synthetic polymer, the second synthetic polymer must contain three or more functional groups in order to obtain a three-dimensional crosslinked network. Most preferably, both the first and the second synthetic polymer contain at least three functional groups.

[0557] Synthetic polymers containing multiple nucleophilic groups are also referred to generically herein as "multi-nucleophilic polymers." For use in the present invention, multi-nucleophilic polymers must contain at least two, more preferably, at least three, nucleophilic groups. If a synthetic polymer containing only two nucleophilic groups is used, a synthetic polymer containing three or more electrophilic groups must be used in order to obtain a three-dimensional crosslinked network.

[0558] Preferred multi-nucleophilic polymers for use in the compositions and methods of the present invention include synthetic polymers that contain, or have been modified to contain, multiple nucleophilic groups such as primary amino groups and thiol groups. Preferred multi-nucleophilic polymers include: (i) synthetic polypeptides that have been synthesized to contain two or more primary amino groups or thiol groups; and (ii) polyethylene glycols that have been modified to contain two or more primary amino groups or thiol groups. In general, reaction of a thiol group with an electrophilic group tends to proceed more slowly than reaction of a primary amino group with an electrophilic group.

[0559] In one embodiment, the multi-nucleophilic polypeptide is a synthetic polypeptide that has been synthesized to incorporate amino acid residues containing primary amino groups (such as lysine) and/or amino acids containing thiol groups (such as cysteine). Poly(lysine), a synthetically produced polymer of the amino acid lysine (145 MW), is particularly preferred. Poly(lysine)s have been prepared having anywhere from 6 to about 4,000 primary amino groups, corresponding to molecular weights of about 870 to about 580,000.

[0560] Poly(lysine)s for use in the present invention preferably have a molecular weight within the range of about 1,000 to about 300,000; more preferably, within the range of about 5,000 to about 100,000; most preferably, within the range of about 8,000 to about 15,000. Poly(lysine)s of varying molecular weights are commercially available from Peninsula Laboratories, Inc. (Belmont, Calif.) and Aldrich Chemical (Milwaukee, Wis.).

[0561] Polyethylene glycol can be chemically modified to contain multiple primary amino or thiol groups according to methods set forth, for example, in Chapter 22 of Poly(ethylene Glycol) Chemistry: Biotechnical and Biomedical Applications, J. Milton Harris, ed., Plenum Press, N.Y. (1992). Polyethylene glycols which have been modified to contain two or more primary amino groups are referred to herein as "multi-amino PEGs." Polyethylene glycols which have been modified to contain two or more thiol groups are referred to herein as "multi-thiol PEGs." As used herein, the term "polyethylene glycol(s)" includes modified and or derivatized polyethylene glycol(s).

[0562] Various forms of multi-amino PEG are commercially available from Shearwater Polymers (Huntsville, Ala.) and from Huntsman Chemical Company (Utah) under the name "Jeffamine." Multi-amino PEGs useful in the present invention include Huntsman's Jeffamine diamines ("D" series) and triamines ("T" series), which contain two and three primary amino groups per molecule, respectively.

[0563] Polyamines such as ethylenediamine (H_2N—CH_2—CH_2—NH_2), tetramethylenediamine (H_2N—$(CH_2)_4$—NH_2), pentamethylenediamine (cadaverine) (H_2N—$(CH_2)_5$—NH_2), hexamethylenediamine (H_2N—$(CH_2)_6$—NH_2), di(2-aminoethyl)amine (HN—(CH_2—CH_2—$NH_2)_2$), and tris(2-aminoethyl)amine (N—(CH_2—CH_2—$NH_2)_3$) may also be used as the synthetic polymer containing multiple nucleophilic groups.

[0564] Synthetic polymers containing multiple electrophilic groups are also referred to herein as "multi-electrophilic polymers." For use in the present invention, the multifunctionally activated synthetic polymers must contain at least two, more preferably, at least three, electrophilic groups in order to form a three-dimensional crosslinked network with multi-nucleophilic polymers. Preferred multi-electrophilic polymers for use in the compositions of the invention are polymers which contain two or more succinimidyl groups capable of forming covalent bonds with nucleophilic groups on other molecules. Succinimidyl groups are highly reactive with materials containing primary amino (NH_2) groups, such as multi-amino PEG, poly(l-ysine), or collagen. Succinimidyl groups are slightly less reactive with materials containing thiol (SH) groups, such as multi-thiol PEG or synthetic polypeptides containing multiple cysteine residues.

[0565] As used herein, the term "containing two or more succinimidyl groups" is meant to encompass polymers which are preferably commercially available containing two or more succinimidyl groups, as well as those that must be chemically derivatized to contain two or more succinimidyl groups. As used herein, the term "succinimidyl group" is intended to encompass sulfosuccinimidyl groups and other such variations of the "generic" succinimidyl group. The presence of the sodium sulfite moiety on the sulfosuccinimidyl group serves to increase the solubility of the polymer.

[0566] Hydrophilic polymers and, in particular, various derivatized polyethylene glycols, are preferred for use in the compositions of the present invention. As used herein, the term "PEG" refers to polymers having the repeating structure (OCH_2—$CH_2)_n$. Structures for some specific, tetrafunctionally activated forms of PEG are shown in FIGS. 4 to 13 of U.S. Pat. No. 5,874,500, incorporated herein by reference. Examples of suitable PEGS include PEG succinimidyl propionate (SE-PEG), PEG succinimidyl succinamide (SSA-PEG), and PEG succinimidyl carbonate (SC-PEG). In one aspect of the invention, the crosslinked matrix is formed in situ by reacting pentaerythritol poly(ethylene glycol)ether tetra-sulfhydryl] (4-armed thiol PEG) and pentaerythritol poly(ethylene glycol)ether tetra-succinimidyl glutaratel (4-armed NHS PEG) as reactive reagents. Structures for these reactants are shown in U.S. Pat. No. 5,874,500. Each

of these materials has a core with a structure that may be seen by adding ethylene oxide-derived residues to each of the hydroxyl groups in pentaerythritol, and then derivatizing the terminal hydroxyl groups (derived from the ethylene oxide) to contain either thiol groups (so as to form 4-armed thiol PEG) or N-hydroxysuccinimydyl groups (so as to form 4-armed NHS PEG), optionally with a linker group present between the ethylene oxide derived backbone and the reactive functional group, where this product is commercially available as COSEAL from Angiotech Pharmaceuticals Inc. Optionally, a group "D" may be present in one or both of these molecules, as discussed in more detail below.

[0567] As discussed above, preferred activated polyethylene glycol derivatives for use in the invention contain succinimidyl groups as the reactive group. However, different activating groups can be attached at sites along the length of the PEG molecule. For example, PEG can be derivatized to form functionally activated PEG propionaldehyde (A-PEG), or functionally activated PEG glycidyl ether (E-PEG), or functionally activated PEG-isocyanate (1-PEG), or functionally activated PEG-vinylsulfone (V-PEG).

[0568] Hydrophobic polymers can also be used to prepare the compositions of the present invention. Hydrophobic polymers for use in the present invention preferably contain, or can be derivatized to contain, two or more electrophilic groups, such as succinimidyl groups, most preferably, two, three, or four electrophilic groups. As used herein, the term "hydrophobic polymer" refers to polymers which contain a relatively small proportion of oxygen or nitrogen atoms.

[0569] Hydrophobic polymers which already contain two or more succinimidyl groups include, without limitation, disuccinimidyl suberate (DSS), bis(sulfosuccinimidyl) suberate (BS3), dithiobis(succinimidylpropionate) (DSP), bis(2-succinimidooxycarbonyloxy) ethyl sulfone (BSOCOES), and 3,3'-dithiobis(sulfosuccinimidylpropionate (DTSPP), and their analogs and derivatives. The above-referenced polymers are commercially available from Pierce (Rockford, Ill.), under catalog Nos. 21555, 21579, 22585, 21554, and 21577, respectively.

[0570] Preferred hydrophobic polymers for use in the invention generally have a carbon chain that is no longer than about 14 carbons. Polymers having carbon chains substantially longer than 14 carbons generally have very poor solubility in aqueous solutions and, as such, have very long reaction times when mixed with aqueous solutions of synthetic polymers containing multiple nucleophilic groups.

[0571] Certain polymers, such as polyacids, can be derivatized to contain two or more functional groups, such as succinimidyl groups. Polyacids for use in the present invention include, without limitation, trimethylolpropane-based tricarboxylic acid, di(trimethylol propane)-based tetracarboxylic acid, heptanedioic acid, octanedioic acid (suberic acid), and hexadecanedioic acid (thapsic acid). Many of these polyacids are commercially available from DuPont Chemical Company (Wilmington, Del.). According to a general method, polyacids can be chemically derivatized to contain two or more succinimidyl groups by reaction with an appropriate molar amount of N-hydroxysuccinimide (NHS) in the presence of N,N'-dicyclohexylcarbodiimide (DCC).

[0572] Polyalcohols such as trimethylolpropane and di(trimethylol propane) can be converted to carboxylic acid form using various methods, then further derivatized by reaction with NHS in the presence of DCC to produce trifunctionally and tetrafunctionally activated polymers, respectively, as described in U.S. application Ser. No. 08/403,358. Polyacids such as heptanedioic acid (HOOC—$(CH_2)_5$—COOH), octanedioic acid (HOOC—$(CH_2)_6$—COOH), and hexadecanedioic acid (HOOC—$(CH_2)_{14}$—COOH) are derivatized by the addition of succinimidyl groups to produce difunctionally activated polymers.

[0573] Polyamines such as ethylenediamine, tetramethylenediamine, pentamethylenediamine (cadaverine), hexamethylenediamine, bis(2-aminoethyl)amine, and tris(2-aminoethyl)amine can be chemically derivatized to polyacids, which can then be derivatized to contain two or more succinimidyl groups by reacting with the appropriate molar amounts of N-hydroxysuccinimide in the presence of DCC, as described in U.S. application Ser. No. 08/403,358. Many of these polyamines are commercially available from DuPont Chemical Company.

[0574] In a preferred embodiment, the first synthetic polymer will contain multiple nucleophilic groups (represented below as "X") and it will react with the second synthetic polymer containing multiple electrophilic groups (represented below as "Y"), resulting in a covalently bound polymer network, as follows:

[0575] Polymer-X_m+Polymer-Y_n→Polymer-Z-Polymer

[0576] wherein $m \geqq 2$, $n \geqq 2$, and $m+n \geqq 5$;

[0577] where exemplary X groups include —NH_2, —SH, —OH, —PH_2, CO—NH—NH_2, etc., where the X groups may be the same or different in polymer-X_m;

[0578] where exemplary Y groups include —CO_2—$N(COCH_2)_2$, —CO_2H, —CHO, —$CHOCH_2$ (epoxide), —N═C═O, —SO_2—CH═CH_2, —$N(COCH)_2$ (i.e., a five-membered heterocyclic ring with a double bond present between the two CH groups), —S—S—(C_5H_4N), etc., where the Y groups may be the same or different in polymer-Y_n; and

[0579] where Z is the functional group resulting from the union of a nucleophilic group (X) and an electrophilic group (Y).

[0580] As noted above, it is also contemplated by the present invention that X and Y may be the same or different, i.e., a synthetic polymer may have two different electrophilic groups, or two different nucleophilic groups, such as with glutathione.

[0581] In one embodiment, the backbone of at least one of the synthetic polymers comprises alkylene oxide residues, e.g., residues from ethylene oxide, propylene oxide, and mixtures thereof. The term 'backbone' refers to a significant portion of the polymer.

[0582] For example, the synthetic polymer containing alkylene oxide residues may be described by the formula X-polymer-X or Y-polymer-Y, wherein X and Y are as defined above, and the term "polymer" represents —$(CH_2CH_2O)_n$— or —$(CH(CH_3)CH_2O)_n$— or —$(CH_2$—CH_2—$O)_n$—$(CH(CH_3)CH_2$—$O)_n$—. In these cases the synthetic polymer would be difunctional.

[0583] The required functional group X or Y is commonly coupled to the polymer backbone by a linking group (rep-

resented below as "Q"), many of which are known or possible. There are many ways to prepare the various functionalized polymers, some of which are listed below:

[0584] Polymer-Q_1-X+Polymer-Q_2-Y→Polymer-Q_1-Z-Q_2-Polymer

[0585] Exemplary Q groups include —O—$(CH_2)_n$—; —S—$(CH_2)_n$—; —NH—$(CH_2)_n$—; —O_2C—NH—$(CH_2)_n$—; —O_2C—$(CH_2)_n$—; —O_2C—$(CR^1H)_n$—; and —O—R_2—CO—NH—, which provide synthetic polymers of the partial structures: polymer-O—$(CH_2)_n$—(X or Y); polymer-S—$(CH_2)_n$—(X or Y); polymer-NH—$(CH_2)_n$—(X or Y); polymer-O_2C—NH—$(CH_2)_n$—(X or Y); polymer-O_2C—$(CH_2)_r$—(X or Y); polymer-O_2C—$(CR^1H)_n$—(X or Y); and polymer-O—R_2—CO—NH—(X or Y), respectively. In these structures, n=1-10, R^1=H or alkyl (i.e., CH_3, C_2H_5, etc.); R^2=CH_2, or CO—NH—CH_2CH_2; and Q_1 and Q_2 may be the same or different.

[0586] For example, when Q_2=OCH_2CH_2 (there is no Q_1 in this case); Y=—CO_2—$N(COCH_2)_2$; and X=—NH_2, —SH, or —OH, the resulting reactions and Z groups would be as follows:

[0587] Polymer-NH_2+Polymer-O—CH_2—CH_2—CO_2—$N(COCH_2)_2$→Polymer-NH—CO—CH_2—CH_2—O-Polymer;

[0588] Polymer-SH+Polymer-O—CH_2—CH_2—CO_2—$N(COCH_2)_2$→Polymer-S—$COCH_2CH_2$—O-Polymer; and

[0589] Polymer-OH+Polymer-O—CH_2—CH_2—CO_2—$N(COCH_2)_2$→Polymer-O—$COCH_2CH_2$—O-Polymer.

[0590] An additional group, represented below as "D", can be inserted between the polymer and the linking group, if present. One purpose of such a D group is to affect the degradation rate of the crosslinked polymer composition in vivo, for example, to increase the degradation rate, or to decrease the degradation rate. This may be useful in many instances, for example, when drug has been incorporated into the matrix, and it is desired to increase or decrease polymer degradation rate so as to influence a drug delivery profile in the desired direction. An illustration of a crosslinking reaction involving first and second synthetic polymers each having D and Q groups is shown below.

[0591] Polymer-D-Q-X+Polymer-D-Q-Y→Polymer-D-Q-Z-Q-D-Polymer

[0592] Some useful biodegradable groups "D" include polymers formed from one or more α-hydroxy acids, e.g., lactic acid, glycolic acid, and the cyclization products thereof (e.g., lactide, glycolide), ϵ-caprolactone, and amino acids. The polymers may be referred to as polylactide, polyglycolide, poly(co-lactide-glycolide); poly-ϵ-caprolactone, polypeptide (also known as poly amino acid, for example, various di- or tri-peptides) and poly(anhydride)s.

[0593] In a general method for preparing the crosslinked polymer compositions used in the context of the present invention, a first synthetic polymer containing multiple nucleophilic groups is mixed with a second synthetic polymer containing multiple electrophilic groups. Formation of a three-dimensional crosslinked network occurs as a result of the reaction between the nucleophilic groups on the first synthetic polymer and the electrophilic groups on the second synthetic polymer.

[0594] The concentrations of the first synthetic polymer and the second synthetic polymer used to prepare the compositions of the present invention will vary depending upon a number of factors, including the types and molecular weights of the particular synthetic polymers used and the desired end use application. In general, when using multi-amino PEG as the first synthetic polymer, it is preferably used at a concentration in the range of about 0.5 to about 20 percent by weight of the final composition, while the second synthetic polymer is used at a concentration in the range of about 0.5 to about 20 percent by weight of the final composition. For example, a final composition having a total weight of 1 gram (1000 milligrams) would contain between about 5 to about 200 milligrams of multi-amino PEG, and between about 5 to about 200 milligrams of the second synthetic polymer.

[0595] Use of higher concentrations of both first and second synthetic polymers will result in the formation of a more tightly crosslinked network, producing a stiffer, more robust gel. Compositions intended for use in tissue augmentation will generally employ concentrations of first and second synthetic polymer that fall toward the higher end of the preferred concentration range. Compositions intended for use as bioadhesives or in adhesion prevention do not need to be as firm and may therefore contain lower polymer concentrations.

[0596] Because polymers containing multiple electrophilic groups will also react with water, the second synthetic polymer is generally stored and used in sterile, dry form to prevent the loss of crosslinking ability due to hydrolysis which typically occurs upon exposure of such electrophilic groups to aqueous media. Processes for preparing synthetic hydrophilic polymers containing multiple electrophylic groups in sterile, dry form are set forth in U.S. Pat. No. 5,643,464. For example, the dry synthetic polymer may be compression molded into a thin sheet or membrane, which can then be sterilized using gamma or, preferably, e-beam irradiation. The resulting dry membrane or sheet can be cut to the desired size or chopped into smaller size particulates. In contrast, polymers containing multiple nucleophilic groups are generally not water-reactive and can therefore be stored in aqueous solution.

[0597] In certain embodiments, one or both of the electrophilic- or nucleophilic-terminated polymers described above can be combined with a synthetic or naturally occurring polymer. The presence of the synthetic or naturally occurring polymer may enhance the mechanical and/or adhesive properties of the in situ forming compositions. Naturally occurring polymers, and polymers derived from naturally occurring polymer that may be included in in situ forming materials include naturally occurring proteins, such as collagen, collagen derivatives (such as methylated collagen), fibrinogen, thrombin, albumin, fibrin, and derivatives of and naturally occurring polysaccharides, such as glycosaminoglycans, including deacetylated and desulfated glycosaminoglycan derivatives.

[0598] In one aspect, a composition comprising naturally-occurring protein and both of the first and second synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising collagen and both of the first and second synthetic polymer as described above is used to form

the crosslinked matrix according to the present invention. In one aspect, a composition comprising methylated collagen and both of the first and second synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising fibrinogen and both of the first and second synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising thrombin and both of the first and second synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising albumin and both of the first and second synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising fibrin and both of the first and second synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising naturally occurring polysaccharide and both of the first and second synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising glycosaminoglycan and both of the first and second synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising deacetylated glycosaminoglycan and both of the first and second synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising desulfated glycosaminoglycan and both of the first and second synthetic polymer as described above is used to form the crosslinked matrix according to the present invention.

[0599] In one aspect, a composition comprising naturally-occurring protein and the first synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising collagen and the first synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising methylated collagen and the first synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising fibrinogen and the first synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising thrombin and the first synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising albumin and the first synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising fibrin and the first synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising naturally occurring polysaccharide and the first synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising glycosaminoglycan and the first synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising deacetylated glycosaminoglycan and the first synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising desulfated glycosaminoglycan and the first synthetic polymer as described above is used to form the crosslinked matrix according to the present invention.

[0600] In one aspect, a composition comprising naturally-occurring protein and the second synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising collagen and the second synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising methylated collagen and the second synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising fibrinogen and the second synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising thrombin and the second synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising albumin and the second synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising fibrin and the second synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising naturally occurring polysaccharide and the second synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising glycosaminoglycan and the second synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising deacetylated glycosaminoglycan and the second synthetic polymer as described above is used to form the crosslinked matrix according to the present invention. In one aspect, a composition comprising desulfated glycosaminoglycan and the second synthetic polymer as described above is used to form the crosslinked matrix according to the present invention.

[0601] The presence of protein or polysaccharide components which contain functional groups that can react with the functional groups on multiple activated synthetic polymers can result in formation of a crosslinked synthetic polymer-naturally occurring polymer matrix upon mixing and/or crosslinking of the synthetic polymer(s). In particular, when the naturally occurring polymer (protein or polysaccharide) also contains nucleophilic groups such as primary amino groups, the electrophilic groups on the second synthetic polymer will react with the primary amino groups on these components, as well as the nucleophilic groups on the first synthetic polymer, to cause these other components to become part of the polymer matrix. For example, lysine-rich proteins such as collagen may be especially reactive with electrophilic groups on synthetic polymers.

[0602] In one aspect, the naturally occurring protein is polymer may be collagen. As used herein, the term "collagen" or "collagen material" refers to all forms of collagen, including those which have been processed or otherwise modified and is intended to encompass collagen of any type, from any source, including, but not limited to, collagen extracted from tissue or produced recombinantly, collagen

analogues, collagen derivatives, modified collagens, and denatured collagens, such as gelatin.

[0603] In general, collagen from any source may be included in the compositions of the invention; for example, collagen may be extracted and purified from human or other mammalian source, such as bovine or porcine corium and human placenta, or may be recombinantly or otherwise produced. The preparation of purified, substantially non-antigenic collagen in solution from bovine skin is well known in the art. U.S. Pat. No. 5,428,022 discloses methods of extracting and purifying collagen from the human placenta. U.S. Pat. No. 5,667,839, discloses methods of producing recombinant human collagen in the milk of transgenic animals, including transgenic cows. Collagen of any type, including, but not limited to, types I, II, III, IV, or any combination thereof, may be used in the compositions of the invention, although type I is generally preferred. Either atelopeptide or telopeptide-containing collagen may be used; however, when collagen from a xenogeneic source, such as bovine collagen, is used, atelopeptide collagen is generally preferred, because of its reduced immunogenicity compared to telopeptide-containing collagen.

[0604] Collagen that has not been previously crosslinked by methods such as heat, irradiation, or chemical crosslinking agents is preferred for use in the compositions of the invention, although previously crosslinked collagen may be used. Non-crosslinked atelopeptide fibrillar collagen is commercially available from Inamed Aesthetics (Santa Barbara, Calif.) at collagen concentrations of 35 mg/ml and 65 mg/ml under the trademarks ZYDERM I Collagen and ZYDERM II Collagen, respectively. Glutaraldehyde crosslinked atelopeptide fibrillar collagen is commercially available from Inamed Corporation (Santa Barbara, Calif.) at a collagen concentration of 35 mg/ml under the trademark ZYPLAST Collagen.

[0605] Collagens for use in the present invention are generally in aqueous suspension at a concentration between about 20 mg/ml to about 120 mg/ml; preferably, between about 30 mg/ml to about 90 mg/ml.

[0606] Because of its tacky consistency, nonfibrillar collagen may be preferred for use in compositions that are intended for use as bioadhesives. The term "nonfibrillar collagen" refers to any modified or unmodified collagen material that is in substantially nonfibrillar form at pH 7, as indicated by optical clarity of an aqueous suspension of the collagen.

[0607] Collagen that is already in nonfibrillar form may be used in the compositions of the invention. As used herein, the term "nonfibrillar collagen" is intended to encompass collagen types that are nonfibrillar in native form, as well as collagens that have been chemically modified such that they are in nonfibrillar form at or around neutral pH. Collagen types that are nonfibrillar (or microfibrillar) in native form include types IV, VI, and VII.

[0608] Chemically modified collagens that are in nonfibrillar form at neutral pH include succinylated collagen and methylated collagen, both of which can be prepared according to the methods described in U.S. Pat. No. 4,164,559, issued Aug. 14, 1979, to Miyata et al., which is hereby incorporated by reference in its entirety. Due to its inherent tackiness, methylated collagen is particularly preferred for use in bioadhesive compositions, as disclosed in U.S. application Ser. No. 08/476,825.

[0609] Collagens for use in the crosslinked polymer compositions of the present invention may start out in fibrillar form, then be rendered nonfibrillar by the addition of one or more fiber disassembly agent. The fiber disassembly agent must be present in an amount sufficient to render the collagen substantially nonfibrillar at pH 7, as described above. Fiber disassembly agents for use in the present invention include, without limitation, various biocompatible alcohols, amino acids (e.g., arginine), inorganic salts (e.g., sodium chloride and potassium chloride), and carbohydrates (e.g., various sugars including sucrose).

[0610] In one aspect, the polymer may be collagen or a collagen derivative, for example methylated collagen. An example of an in situ forming composition uses pentaerythritol poly(ethylene glycol)ether tetra-sulfhydryl] (4-armed thiol PEG), pentaerythritol poly(ethylene glycol)ether tetra-succinimidyl glutarate] (4-armed NHS PEG) and methylated collagen as the reactive reagents. This composition, when mixed with the appropriate buffers can produce a crosslinked hydrogel. (See, e.g., U.S. Pat. Nos. 5,874,500; 6,051,648; 6,166,130; 5,565,519 and 6,312,725).

[0611] In another aspect, the naturally occurring polymer may be a glycosaminoglycan. Glycosaminoglycans, e.g., hyaluronic acid, contain both anionic and cationic functional groups along each polymeric chain, which can form intramolecular and/or intermolecular ionic crosslinks, and are responsible for the thixotropic (or shear thinning) nature of hyaluronic acid.

[0612] In certain aspects, the glycosaminoglycan may be derivatized. For example, glycosaminoglycans can be chemically derivatized by, e.g., deacetylation, desulfation, or both in order to contain primary amino groups available for reaction with electrophilic groups on synthetic polymer molecules. Glycosaminoglycans that can be derivatized according to either or both of the aforementioned methods include the following: hyaluronic acid, chondroitin sulfate A, chondroitin sulfate B (dermatan sulfate), chondroitin sulfate C, chitin (can be derivatized to chitosan), keratan sulfate, keratosulfate, and heparin. Derivatization of glycosaminoglycans by deacetylation and/or desulfation and covalent binding of the resulting glycosaminoglycan derivatives with synthetic hydrophilic polymers is described in further detail in commonly assigned, allowed U.S. patent application Ser. No. 08/146,843, filed Nov. 3, 1993.

[0613] In general, the collagen is added to the first synthetic polymer, then the collagen and first synthetic polymer are mixed thoroughly to achieve a homogeneous composition. The second synthetic polymer is then added and mixed into the collagen/first synthetic polymer mixture, where it will covalently bind to primary amino groups or thiol groups on the first synthetic polymer and primary amino groups on the collagen, resulting in the formation of a homogeneous crosslinked network. Various deacetylated and/or desulfated glycosaminoglycan derivatives can be incorporated into the composition in a similar manner as that described above for collagen. In addition, the introduction of hydrocolloids such as carboxymethylcellulose may promote tissue adhesion and/or swellability.

[0614] Administration of the Crosslinked Synthetic Polymer Compositions

[0615] The compositions of the present invention having two synthetic polymers may be administered before, during

or after crosslinking of the first and second synthetic polymer. Certain uses, which are discussed in greater detail below, such as tissue augmentation, may require the compositions to be crosslinked before administration, whereas other applications, such as tissue adhesion, require the compositions to be administered before crosslinking has reached "equilibrium." The point at which crosslinking has reached equilibrium is defined herein as the point at which the composition no longer feels tacky or sticky to the touch.

[0616] In order to administer the composition prior to crosslinking, the first synthetic polymer and second synthetic polymer may be contained within separate barrels of a dual-compartment syringe. In this case, the two synthetic polymers do not actually mix until the point at which the two polymers are extruded from the tip of the syringe needle into the patient's tissue. This allows the vast majority of the crosslinking reaction to occur in situ, avoiding the problem of needle blockage which commonly occurs if the two synthetic polymers are mixed too early and crosslinking between the two components is already too advanced prior to delivery from the syringe needle. The use of a dual-compartment syringe, as described above, allows for the use of smaller diameter needles, which is advantageous when performing soft tissue augmentation in delicate facial tissue, such as that surrounding the eyes.

[0617] Alternatively, the first synthetic polymer and second synthetic polymer may be mixed according to the methods described above prior to delivery to the tissue site, then injected to the desired tissue site immediately (preferably, within about 60 seconds) following mixing.

[0618] In another embodiment of the invention, the first synthetic polymer and second synthetic polymer are mixed, then extruded and allowed to crosslink into a sheet or other solid form. The crosslinked solid is then dehydrated to remove substantially all unbound water. The resulting dried solid may be ground or comminuted into particulates, then suspended in a nonaqueous fluid carrier, including, without limitation, hyaluronic acid, dextran sulfate, dextran, succinylated noncrosslinked collagen, methylated noncrosslinked collagen, glycogen, glycerol, dextrose, maltose, triglycerides of fatty acids (such as corn oil, soybean oil, and sesame oil), and egg yolk phospholipid. The suspension of particulates can be injected through a small-gauge needle to a tissue site. Once inside the tissue, the crosslinked polymer particulates will rehydrate and swell in size at least five-fold.

[0619] Hydrophilic Polymer+Plurality of Crosslinkable Components

[0620] As mentioned above, the first and/or second synthetic polymers may be combined with a hydrophilic polymer, e.g., collagen or methylated collagen, to form a composition useful in the present invention. In one general embodiment, the compositions useful in the present invention include a hydrophilic polymer in combination with two or more crosslinkable components. This embodiment is described in further detail in this section.

[0621] The Hydrophilic Polymer Component:

[0622] The hydrophilic polymer component may be a synthetic or naturally occurring hydrophilic polymer. Naturally occurring hydrophilic polymers include, but are not limited to: proteins such as collagen and derivatives thereof, fibronectin, albumins, globulins, fibrinogen, and fibrin, with collagen particularly preferred; carboxylated polysaccharides such as polymannuronic acid and polygalacturonic acid; aminated polysaccharides, particularly the glycosaminoglycans, e.g., hyaluronic acid, chitin, chondroitin sulfate A, B, or C, keratin sulfate, keratosulfate and heparin; and activated polysaccharides such as dextran and starch derivatives. Collagen (e.g., methylated collagen) and glycosaminoglycans are preferred naturally occurring hydrophilic polymers for use herein.

[0623] In general, collagen from any source may be used in the composition of the method; for example, collagen may be extracted and purified from human or other mammalian source, such as bovine or porcine corium and human placenta, or may be recombinantly or otherwise produced. The preparation of purified, substantially non-antigenic collagen in solution from bovine skin is well known in the art. See, e.g., U.S. Pat. No. 5,428,022, to Palefsky et al., which discloses methods of extracting and purifying collagen from the human placenta. See also U.S. Pat. No. 5,667,839, to Berg, which discloses methods of producing recombinant human collagen in the milk of transgenic animals, including transgenic cows. Unless otherwise specified, the term "collagen" or "collagen material" as used herein refers to all forms of collagen, including those that have been processed or otherwise modified.

[0624] Collagen of any type, including, but not limited to, types I, II, III, IV, or any combination thereof, may be used in the compositions of the invention, although type I is generally preferred. Either atelopeptide or telopeptide-containing collagen may be used; however, when collagen from a source, such as bovine collagen, is used, atelopeptide collagen is generally preferred, because of its reduced immunogenicity compared to telopeptide-containing collagen.

[0625] Collagen that has not been previously crosslinked by methods such as heat, irradiation, or chemical crosslinking agents is preferred for use in the compositions of the invention, although previously crosslinked collagen may be used. Non-crosslinked atelopeptide fibrillar collagen is commercially available from McGhan Medical Corporation (Santa Barbara, Calif.) at collagen concentrations of 35 mg/ml and 65 mg/ml under the trademarks ZYDERM® I Collagen and ZYDERM® II Collagen, respectively. Glutaraldehyde-crosslinked atelopeptide fibrillar collagen is commercially available from McGhan Medical Corporation at a collagen concentration of 35 mg/ml under the trademark ZYPLAST®.

[0626] Collagens for use in the present invention are generally, although not necessarily, in aqueous suspension at a concentration between about 20 mg/ml to about 120 mg/ml, preferably between about 30 mg/ml to about 90 mg/ml.

[0627] Although intact collagen is preferred, denatured collagen, commonly known as gelatin, can also be used in the compositions of the invention. Gelatin may have the added benefit of being degradable faster than collagen.

[0628] Because of its greater surface area and greater concentration of reactive groups, nonfibrillar collagen is generally preferred. The term "nonfibrillar collagen" refers to any modified or unmodified collagen material that is in substantially nonfibrillar form at pH 7, as indicated by optical clarity of an aqueous suspension of the collagen.

[0629] Collagen that is already in nonfibrillar form may be used in the compositions of the invention. As used herein, the term "nonfibrillar collagen" is intended to encompass collagen types that are nonfibrillar in native form, as well as collagens that have been chemically modified such that they are in nonfibrillar form at or around neutral pH. Collagen types that are nonfibrillar (or microfibrillar) in native form include types IV, VI, and VII.

[0630] Chemically modified collagens that are in nonfibrillar form at neutral pH include succinylated collagen, propylated collagen, ethylated collagen, methylated collagen, and the like, both of which can be prepared according to the methods described in U.S. Pat. No. 4,164,559, to Miyata et al., which is hereby incorporated by reference in its entirety. Due to its inherent tackiness, methylated collagen is particularly preferred, as disclosed in U.S. Pat. No. 5,614,587 to Rhee et al.

[0631] Collagens for use in the crosslinkable compositions of the present invention may start out in fibrillar form, then be rendered nonfibrillar by the addition of one or more fiber disassembly agents. The fiber disassembly agent must be present in an amount sufficient to render the collagen substantially nonfibrillar at pH 7, as described above. Fiber disassembly agents for use in the present invention include, without limitation, various biocompatible alcohols, amino acids, inorganic salts, and carbohydrates, with biocompatible alcohols being particularly preferred. Preferred biocompatible alcohols include glycerol and propylene glycol. Non-biocompatible alcohols, such as ethanol, methanol, and isopropanol, are not preferred for use in the present invention, due to their potentially deleterious effects on the body of the patient receiving them. Preferred amino acids include arginine. Preferred inorganic salts include sodium chloride and potassium chloride. Although carbohydrates, such as various sugars including sucrose, may be used in the practice of the present invention, they are not as preferred as other types of fiber disassembly agents because they can have cytotoxic effects in vivo.

[0632] As fibrillar collagen has less surface area and a lower concentration of reactive groups than nonfibrillar, fibrillar collagen is less preferred. However, as disclosed in U.S. Pat. No. 5,614,587, fibrillar collagen, or mixtures of nonfibrillar and fibrillar collagen, may be preferred for use in compositions intended for long-term persistence in vivo, if optical clarity is not a requirement.

[0633] Synthetic hydrophilic polymers may also be used in the present invention. Useful synthetic hydrophilic polymers include, but are not limited to: polyalkylene oxides, particularly polyethylene glycol and poly(ethylene oxide)-poly(propylene oxide) copolymers, including block and random copolymers; polyols such as glycerol, polyglycerol (particularly highly branched polyglycerol), propylene glycol and trimethylene glycol substituted with one or more polyalkylene oxides, e.g., mono-, di- and tri-polyoxyethylated glycerol, mono- and di-polyoxyethylated propylene glycol, and mono- and di-polyoxyethylated trimethylene glycol; polyoxyethylated sorbitol, polyoxyethylated glucose; acrylic acid polymers and analogs and copolymers thereof, such as polyacrylic acid per se, polymethacrylic acid, poly(hydroxyethyl-methacrylate), poly(hydroxyethylacrylate), poly(methylalkylsulfoxide methacrylate), poly-(methylalkylsulfoxide acrylate) and copolymers of any of the foregoing, and/or with additional acrylate species such as aminoethyl acrylate and mono-2-(acryloxy)-ethyl succinate; polymaleic acid; poly(acrylamides) such as polyacrylamide per se, poly(methacrylamide), poly(dimethylacrylamide), and poly(N-isopropyl-acrylamide); poly(olefinic alcohol)s such as poly(vinyl alcohol); poly(N-vinyl lactams) such as poly(vinyl pyrrolidone), poly(N-vinyl caprolactam), and copolymers thereof; polyoxazolines, including poly(methyloxazoline) and poly(ethyloxazoline); and polyvinylamines. It must be emphasized that the aforementioned list of polymers is not exhaustive, and a variety of other synthetic hydrophilic polymers may be used, as will be appreciated by those skilled in the art.

[0634] The Crosslinkable Components:

[0635] The compositions of the invention also comprise a plurality of crosslinkable components. Each of the crosslinkable components participates in a reaction that results in a crosslinked matrix. Prior to completion of the crosslinking reaction, the crosslinkable components provide the necessary adhesive qualities that enable the methods of the invention.

[0636] The crosslinkable components are selected so that crosslinking gives rise to a biocompatible, nonimmunogenic matrix useful in a variety of contexts including adhesion prevention, biologically active agent delivery, tissue augmentation, and other applications. The crosslinkable components of the invention comprise: a component A, which has m nucleophilic groups, wherein $m \geqq 2$ and a component B, which has n electrophilic groups capable of reaction with the m nucleophilic groups, wherein $n \geqq 2$ and $m+n \geqq 4$. An optional third component, optional component C, which has at least one functional group that is either electrophilic and capable of reaction with the nucleophilic groups of component A, or nucleophilic and capable of reaction with the electrophilic groups of component B may also be present. Thus, the total number of functional groups present on components A, B and C, when present, in combination is $\geqq 5$; that is, the total functional groups given by m+n+p must be $\geqq 5$, where p is the number of functional groups on component C and, as indicated, is $\geqq 1$. Each of the components is biocompatible and nonimmunogenic, and at least one component is comprised of a hydrophilic polymer. Also, as will be appreciated, the composition may contain additional crosslinkable components D, E, F, etc., having one or more reactive nucleophilic or electrophilic groups and thereby participate in formation of the crosslinked biomaterial via covalent bonding to other components.

[0637] The m nucleophilic groups on component A may all be the same, or, alternatively, A may contain two or more different nucleophilic groups. Similarly, the n electrophilic groups on component B may all be the same, or two or more different electrophilic groups may be present. The functional group(s) on optional component C, if nucleophilic, may or may not be the same as the nucleophilic groups on component A, and, conversely, if electrophilic, the functional group(s) on optional component C may or may not be the same as the electrophilic groups on component B.

[0638] Accordingly, the components may be represented by the structural formulae

$R^1(-[Q^1]_q-X)_m$ (component A), (I)

$R^2(-[Q^2]_r-Y)_n$ (component B), and (II)

$R^3(-[Q^3]_s-Fn)_p$ (optional component C), (III)

[0639] wherein:

[0640] R_1, R^2 and R^3 are independently selected from the group consisting of C_2 to C_{14} hydrocarbyl, heteroatom-containing C_2 to C_{14} hydrocarbyl, hydrophilic polymers, and hydrophobic polymers, providing that at least one of R_1, R^2 and R^3 is a hydrophilic polymer, preferably a synthetic hydrophilic polymer;

[0641] X represents one of the m nucleophilic groups of component A, and the various X moieties on A may be the same or different;

[0642] Y represents one of the n electrophilic groups of component B, and the various Y moieties on A may be the same or different;

[0643] Fn represents a functional group on optional component C;

[0644] Q^1, Q^2 and Q^3 are linking groups;

[0645] $m \geqq 2$, $n \geqq 2$, $m+n$ is $\geqq 4$, q, and r are independently zero or 1, and when optional component C is present, $p \geqq 1$, and s is independently zero or 1.

[0646] Reactive Groups:

[0647] X may be virtually any nucleophilic group, so long as reaction can occur with the electrophilic group Y. Analogously, Y may be virtually any electrophilic group, so long as reaction can take place with X. The only limitation is a practical one, in that reaction between X and Y should be fairly rapid and take place automatically upon admixture with an aqueous medium, without need for heat or potentially toxic or non-biodegradable reaction catalysts or other chemical reagents. It is also preferred although not essential that reaction occur without need for ultraviolet or other radiation. Ideally, the reactions between X and Y should be complete in under 60 minutes, preferably under 30 minutes. Most preferably, the reaction occurs in about 5 to 15 minutes or less.

[0648] Examples of nucleophilic groups suitable as X include, but are not limited to, $—NH_2$, $—NHR^4$, $—N(R^4)_2$, —SH, —OH, —COOH, $—C_6H_4—OH$, $—PH_2$, $—PHR^5$, $—P(R^5)_2$, $—NH—NH_2$, $—CO—NH—NH_2$, $—C_5H_4N$, etc. wherein R^4 and R^5 are hydrocarbyl, typically alkyl or monocyclic aryl, preferably alkyl, and most preferably lower alkyl. Organometallic moieties are also useful nucleophilic groups for the purposes of the invention, particularly those that act as carbanion donors. Organometallic nucleophiles are not, however, preferred. Examples of organometallic moieties include: Grignard functionalities $—R^6MgHal$ wherein R^6 is a carbon atom (substituted or unsubstituted), and Hal is halo, typically bromo, iodo or chloro, preferably bromo; and lithium-containing functionalities, typically alkyllithium groups; sodium-containing functionalities.

[0649] It will be appreciated by those of ordinary skill in the art that certain nucleophilic groups must be activated with a base so as to be capable of reaction with an electrophile. For example, when there are nucleophilic sulfhydryl and hydroxyl groups in the crosslinkable composition, the composition must be admixed with an aqueous base in order to remove a proton and provide an $—S^-$ or $—O^-$ species to enable reaction with an electrophile. Unless it is desirable for the base to participate in the crosslinking reaction, a nonnucleophilic base is preferred. In some embodiments, the base may be present as a component of a buffer solution. Suitable bases and corresponding crosslinking reactions are described infra.

[0650] The selection of electrophilic groups provided within the crosslinkable composition, i.e., on component B, must be made so that reaction is possible with the specific nucleophilic groups. Thus, when the X moieties are amino groups, the Y groups are selected so as to react with amino groups. Analogously, when the X moieties are sulfhydryl moieties, the corresponding electrophilic groups are sulfhydryl-reactive groups, and the like.

[0651] By way of example, when X is amino (generally although not necessarily primary amino), the electrophilic groups present on Y are amino reactive groups such as, but not limited to: (1) carboxylic acid esters, including cyclic esters and "activated" esters; (2) acid chloride groups (—CO—Cl); (3) anhydrides (—(CO)—O—(CO)—R); (4) ketones and aldehydes, including α,β-unsaturated aldehydes and ketones such as —CH═CH—CH═O and $—CH═CH—C(CH_3)═O$; (5) halides; (6) isocyanate (—N═C═O); (7) isothiocyanate (—N═C═S); (8) epoxides; (9) activated hydroxyl groups (e.g., activated with conventional activating agents such as carbonyldiimidazole or sulfonyl chloride); and (10) olefins, including conjugated olefins, such as ethenesulfonyl ($—SO_2CH═CH_2$) and analogous functional groups, including acrylate ($—CO_2—C═CH_2$), methacrylate ($—CO_2—C(CH_3)═CH_2$)), ethyl acrylate ($—CO_2—C(CH_2CH_3)═CH_2$), and ethyleneimino (—CH═CH—C═NH). Since a carboxylic acid group per se is not susceptible to reaction with a nucleophilic amine, components containing carboxylic acid groups must be activated so as to be amine-reactive. Activation may be accomplished in a variety of ways, but often involves reaction with a suitable hydroxyl-containing compound in the presence of a dehydrating agent such as dicyclohexylcarbodiimide (DCC) or dicyclohexylurea (DHU). For example, a carboxylic acid can be reacted with an alkoxy-substituted N-hydroxy-succinimide or N-hydroxysulfosuccinimide in the presence of DCC to form reactive electrophilic groups, the N-hydroxysuccinimide ester and the N-hydroxysulfosuccinimide ester, respectively. Carboxylic acids may also be activated by reaction with an acyl halide such as an acyl chloride (e.g., acetyl chloride), to provide a reactive anhydride group. In a further example, a carboxylic acid may be converted to an acid chloride group using, e.g., thionyl chloride or an acyl chloride capable of an exchange reaction. Specific reagents and procedures used to carry out such activation reactions will be known to those of ordinary skill in the art and are described in the pertinent texts and literature.

[0652] Analogously, when X is sulfhydryl, the electrophilic groups present on Y are groups that react with a sulfhydryl moiety. Such reactive groups include those that form thioester linkages upon reaction with a sulfhydryl group, such as those described in PCT Publication No. WO 00/62827 to Wallace et al. *As explained in detail therein, such "sulfhydryl reactive" groups include, but are not*

limited to: mixed anhydrides; ester derivatives of phosphorus; ester derivatives of p-nitrophenol, p-nitrothiophenol and pentafluorophenol; esters of substituted hydroxylamines, including N-hydroxyphthalimide esters, N-hydroxysuccinimide esters, N-hydroxysulfosuccinimide esters, and N-hydroxyglutarimide esters; esters of 1-hydroxybenzotriazole; 3-hydroxy-3,4-dihydro-benzotriazin-4-one; 3-hydroxy-3,4-dihydro-quinazoline-4-one; carbonylimidazole derivatives; acid chlorides; ketenes; and isocyanates. With these sulfhydryl reactive groups, auxiliary reagents can also be used to facilitate bond formation, e.g., 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide can be used to facilitate coupling of sulfhydryl groups to carboxyl-containing groups.

[0653] In addition to the sulfhydryl reactive groups that form thioester linkages, various other sulfhydryl reactive functionalities can be utilized that form other types of linkages. For example, compounds that contain methyl imidate derivatives form imido-thioester linkages with sulfhydryl groups. Alternatively, sulfhydryl reactive groups can be employed that form disulfide bonds with sulfhydryl groups; such groups generally have the structure —S—S—Ar where Ar is a substituted or unsubstituted nitrogen-containing heteroaromatic moiety or a non-heterocyclic aromatic group substituted with an electron-withdrawing moiety, such that Ar may be, for example, 4-pyridinyl, o-nitrophenyl, m-nitrophenyl, p-nitrophenyl, 2,4-dinitrophenyl, 2-nitro-4-benzoic acid, 2-nitro-4-pyridinyl, etc. In such instances, auxiliary reagents, i.e., mild oxidizing agents such as hydrogen peroxide, can be used to facilitate disulfide bond formation.

[0654] Yet another class of sulfhydryl reactive groups forms thioether bonds with sulfhydryl groups. Such groups include, inter alia, maleimido, substituted maleimido, haloalkyl, epoxy, imino, and aziridino, as well as olefins (including conjugated olefins) such as ethenesulfonyl, etheneimino, acrylate, methacrylate, and α,β-unsaturated aldehydes and ketones. This class of sulfhydryl reactive groups are particularly preferred as the thioether bonds may provide faster crosslinking and longer in vivo stability.

[0655] When X is —OH, the electrophilic functional groups on the remaining component(s) must react with hydroxyl groups. The hydroxyl group may be activated as described above with respect to carboxylic acid groups, or it may react directly in the presence of base with a sufficiently reactive electrophile such as an epoxide group, an aziridine group, an acyl halide, or an anhydride.

[0656] When X is an organometallic nucleophile such as a Grignard functionality or an alkyllithium group, suitable electrophilic functional groups for reaction therewith are those containing carbonyl groups, including, by way of example, ketones and aldehydes.

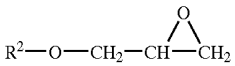
[0657] It will also be appreciated that certain functional groups can react as nucleophiles or as electrophiles, depending on the selected reaction partner and/or the reaction conditions. For example, a carboxylic acid group can act as a nucleophile in the presence of a fairly strong base, but generally acts as an electrophile allowing nucleophilic attack at the carbonyl carbon and concomitant replacement of the hydroxyl group with the incoming nucleophile.

[0658] The covalent linkages in the crosslinked structure that result upon covalent binding of specific nucleophilic components to specific electrophilic components in the crosslinkable composition include, solely by way of example, the following (the optional linking groups Q^1 and Q^2 are omitted for clarity):

TABLE

REPRESENTATIVE NUCLEOPHILIC COMPONENT (A, optional component C element FN_{NU})	REPRESENTATIVE ELECTROPHILIC COMPONENT (B, FN_{EL})	RESULTING LINKAGE
R^1—NH_2	R^2—O—(CO)—O—$N(COCH_2)$ (succinimidyl carbonate terminus)	R^1—NH—(CO)—O—R^2
R^1—SH	R^2—O—(CO)—O—$N(COCH_2)$	R^1—S—(CO)—O—R^2
R^1—OH	R^2—O—(CO)—O—$N(COCH_2)$	R^1—O—(CO)—R^2
R^1—NH_2	R^2—O(CO)—CH=CH_2 (acrylate terminus)	R^1—NH—CH_2CH_2—(CO)—O—R^2
R^1—SH	R^2—O—(CO)—CH=CH_2	R^1—S—CH_2CH_2—(CO)—O—R^2
R^1—OH	R^2—O—(CO)—CH=CH_2	R^1—O—CH_2CH_2—(CO)—O—R^2
R^1—NH_2	R^2—O(CO)—$(CH_2)_3$—CO_2—$N(COCH_2)$ (succinimidyl glutarate terminus)	R^1—NH—(CO)—$(CH_2)_3$—(CO)—OR^2
R^1—SH	R^2—O(CO)—$(CH_2)_3$—CO_2—$N(COCH_2)$	R^1—S—(CO)—$(CH_2)_3$—(CO)—OR^2
R^1—OH	R^2—O(CO)—$(CH_2)_3$—CO_2—$N(COCH_2)$	R^1—O—(CO)—$(CH_2)_3$—(CO)—OR^2
R^1—NH_2	R^2—O—CH_2—CO_2—$N(COCH_2)$ (succinimidyl acetate terminus)	R^1—NH—(CO)—CH_2—OR^2
R^1—SH	R^2—O—CH_2—CO_2—$N(COCH_2)$	R^1—S—(CO)—CH_2—OR^2
R^1—OH	R^2—O—CH_2—CO_2—$N(COCH_2)$	R^1—O—(CO)—CH_2—OR^2
R^1—NH_2	R^2—O—NH(CO)—$(CH_2)_2$—CO_2—$N(COCH_2)$	R^1—NH—(CO)—$(CH_2)_2$—(CO)—NH—OR

TABLE-continued

REPRESENTATIVE NUCLEOPHILIC COMPONENT (A, optional component C element FN_{NU})	REPRESENTATIVE ELECTROPHILIC COMPONENT (B, FN_{EL})	RESULTING LINKAGE
	(succinimidyl succinamide terminus)	
R^1—SH	R^2—O—NH(CO)—$(CH_2)_2$—CO_2—N($COCH_2$)	R^1—S—(CO)—$(CH_2)_2$—(CO)—NH—OR^2
R^1—OH	R^2—O—NH(CO)—$(CH_2)_2$—CO_2—N($COCH_2$)	R^1—O—(CO)—$(CH_2)_2$—(CO)—NH—OR^2
R^1—NH_2	R^2—O—$(CH_2)_2$—CHO (propionaldehyde terminus)	R^1—NH—(CO)—$(CH_2)_2$—OR^2
R^1—NH_2	 (glycidyl ether terminus)	R^1—NH—CH_2—CH(OH)—CH_2—OR^2 and R^1—N[CH_2—CH(OH)—CH_2—OR_2]$_2$
R^1—NH_2	R^2—O—$(CH_2)_2$—N=C=O (isocyanate terminus)	R^1—NH—(CO)—NH—CH_2—OR^2
R^1—NH_2	R^2—SO_2—CH=CH_2 (vinyl sulfone terminus)	R^1—NH—CH_2CH_2—SO_2—R^2
R^1—SH	R^2—SO_2—CH=CH_2	R^1—S—CH_2CH_2—SO_2—R^2

[0659] Linking Groups:

[0660] The functional groups X and Y and FN on optional component C may be directly attached to the compound core (R^1, R^2 or R^3 on optional component C, respectively), or they may be indirectly attached through a linking group, with longer linking groups also termed "chain extenders." In structural formulae (I), (II) and (III), the optional linking groups are represented by Q^1, Q^2 and Q^3, wherein the linking groups are present when q, r and s are equal to 1 (with R, X, Y, Fn, m n and p as defined previously).

[0661] Suitable linking groups are well known in the art. See, for example, International Patent Publication No. WO 97/22371. Linking groups are useful to avoid steric hindrance problems that are sometimes associated with the formation of direct linkages between molecules. Linking groups may additionally be used to link several multifunctionally activated compounds together to make larger molecules. In a preferred embodiment, a linking group can be used to alter the degradative properties of the compositions after administration and resultant gel formation. For example, linking groups can be incorporated into components A, B, or optional component C to promote hydrolysis, to discourage hydrolysis, or to provide a site for enzymatic degradation.

[0662] Examples of linking groups that provide hydrolyzable sites, include, inter alia: ester linkages; anhydride linkages, such as obtained by incorporation of glutarate and succinate; ortho ester linkages; ortho carbonate linkages such as trimethylene carbonate; amide linkages; phosphoester linkages; α-hydroxy acid linkages, such as may be obtained by incorporation of lactic acid and glycolic acid; lactone-based linkages, such as may be obtained by incorporation of caprolactone, valerolactone, γ-butyrolactone and p-dioxanone; and amide linkages such as in a dimeric, oligomeric, or poly(amino acid) segment. Examples of non-degradable linking groups include succinimide, propionic acid and carboxymethylate linkages. See, for example, PCT WO 99/07417. Examples of enzymatically degradable linkages include Leu-Gly-Pro-Ala, which is degraded by collagenase; and Gly-Pro-Lys, which is degraded by plasmin.

[0663] Linking groups can also enhance or suppress the reactivity of the various nucleophilic and electrophilic groups. For example, electron-withdrawing groups within one or two carbons of a sulfhydryl group would be expected to diminish its effectiveness in coupling, due to a lowering of nucleophilicity. Carbon-carbon double bonds and carbonyl groups will also have such an effect. Conversely, electron-withdrawing groups adjacent to a carbonyl group (e.g., the reactive carbonyl of glutaryl-N-hydroxysuccinimidyl) would increase the reactivity of the carbonyl carbon with respect to an incoming nucleophile. By contrast, sterically bulky groups in the vicinity of a functional group can be used to diminish reactivity and thus coupling rate as a result of steric hindrance.

[0664] By way of example, particular linking groups and corresponding component structure are indicated in the following Table:

TABLE

LINKING GROUP	COMPONENT STRUCTURE
—O—$(CH_2)_n$—	Component A: R^1—O—$(CH_2)_n$—X Component B: R^2—O—$(CH_2)_n$—Y Optional Component C: R^3—O—$(CH_2)_n$—Z

TABLE-continued

LINKING GROUP	COMPONENT STRUCTURE
—S—$(CH_2)_n$—	Component A: R^1—S—$(CH_2)_n$—X Component B: R^2—S—$(CH_2)_n$—Y Optional Component C: R^3—S—$(CH_2)_n$—Z
—NH—$(CH_2)_n$—	Component A: R^1—NH—$(CH_2)_n$—X Component B: R^2—NH—$(CH_2)_n$—Y Optional Component C: R^3—NH—$(CH_2)_n$—Z
—O—(CO)—NH—$(CH_2)_n$—	Component A: R^1—O—(CO)—NH—$(CH_2)_n$—X Component B: R^2—O—(CO)—NH—$(CH_2)_n$—Y Optional Component C: R^3—O—(CO)—NH—$(CH_2)_n$—Z
—NH—(CO)—O—$(CH_2)_n$—	Component A: R^1—NH—(CO)—O—$(CH_2)_n$—X Component B: R^2—NH—(CO)—O—$(CH_2)_n$—Y Optional Component C: R^3—NH—(CO)—O—$(CH_2)_n$—Z
—O—(CO)—$(CH_2)_n$—	Component A: R^1—O—(CO)—$(CH_2)_n$—X Component B: R^2—O—(CO)—$(CH_2)_n$—Y Optional Component C: R^3—O—(CO)—$(CH_2)_n$—Z
—(CO)—O—$(CH_2)_n$—	Component A: R^1—(CO)—O—$(CH_2)_n$—X Component B: R^2—(CO)—O—$(CH_2)_n$—Y Optional Component C: R^3—(CO)—O—$(CH_2)_n$—Z
—O—(CO)—O—$(CH_2)_n$—	Component A: R^1—O—(CO)—O—$(CH_2)_n$—X Component B: R^2—O—(CO)—O—$(CH_2)_n$—Y Optional Component C: R^3—O—(CO)—O—$(CH_2)_n$—Z
—O—(CO)—CHR^7—	Component A: R^1—O—(CO)—CHR^7—X Component B: R^2—O—(CO)—CHR^7—Y Optional Component C: R^3—O—(CO)—CHR^7—Z
—O—R^8—(CO)—NH—	Component A: R^1—O—R^8—(CO)—NH—X Component B: R^2—O—R^8—(CO)—NH—Y Optional Component C: R^1—O—R^8—(CO)—NH—X

[0665] In the above Table, n is generally in the range of 1 to about 10, R^7 is generally hydrocarbyl, typically alkyl or aryl, preferably alkyl, and most preferably lower alkyl, and R^8 is hydrocarbylene, heteroatom-containing hydrocarbylene, substituted hydrocarbylene, or substituted heteroatom-containing hydrocarbylene) typically alkylene or arylene (again, optionally substituted and/or containing a heteroatom), preferably lower alkylene (e.g., methylene, ethylene, n-propylene, n-butylene, etc.), phenylene, or amidoalkylene (e.g., —(CO)—NH—CH_2).

[0666] Other general principles that should be considered with respect to linking groups are as follows: If higher molecular weight components are to be used, they preferably have biodegradable linkages as described above, so that fragments larger than 20,000 mol. wt. are not generated during resorption in the body. In addition, to promote water miscibility and/or solubility, it may be desired to add sufficient electric charge or hydrophilicity. Hydrophilic groups can be easily introduced using known chemical synthesis, so long as they do not give rise to unwanted swelling or an undesirable decrease in compressive strength. In particular, polyalkoxy segments may weaken gel strength.

[0667] The Component Core:

[0668] The "core" of each crosslinkable component is comprised of the molecular structure to which the nucleophilic or electrophilic groups are bound. Using the formulae (I) R^1-$[Q^1]_q$-$X)_m$, for component A, (II) R^2(-$[Q^2]_r$-$Y)_n$ for component B, and (III)

[0669] R^3(-$[Q^3]_s$-$Fn)_p$ for optional component C, the "core" groups are R_1, R^2 and R^3. Each molecular core of the reactive components of the crosslinkable composition is generally selected from synthetic and naturally occurring hydrophilic polymers, hydrophobic polymers, and C_2-C_{14} hydrocarbyl groups zero to 2 heteroatoms selected from N, O and S, with the proviso that at least one of the crosslinkable components A, B, and optionally C, comprises a molecular core of a synthetic hydrophilic polymer. In a preferred embodiment, at least one of A and B comprises a molecular core of a synthetic hydrophilic polymer.

[0670] Hydrophilic Crosslinkable Components

[0671] In one aspect, the crosslinkable component(s) is (are) hydrophilic polymers. The term "hydrophilic polymer" as used herein refers to a synthetic polymer having an average molecular weight and composition effective to render the polymer "hydrophilic" as defined above. As discussed above, synthetic crosslinkable hydrophilic polymers useful herein include, but are not limited to: polyalkylene oxides, particularly polyethylene glycol and poly(ethylene oxide)-poly(propylene oxide) copolymers, including block and random copolymers; polyols such as glycerol, polyglycerol (particularly highly branched polyglycerol), propylene glycol and trimethylene glycol substituted with one or more polyalkylene oxides, e.g., mono-, di- and tri-polyoxyethylated glycerol, mono- and di-polyoxyethylated propylene glycol, and mono- and di-polyoxyethylated trimethylene glycol; polyoxyethylated sorbitol, polyoxyethylated glucose; acrylic acid polymers and analogs and copolymers thereof, such as polyacrylic acid per se, polymethacrylic acid, poly(hydroxyethyl-methacrylate), poly(hydroxyethylacrylate), poly(methylalkylsulfoxide methacrylate), poly(methylalkylsulfoxide acrylate) and copolymers of any of the foregoing, and/or with additional acrylate species such as aminoethyl acrylate and mono-2-(acryloxy)-ethyl succinate; polymaleic acid; poly(acrylamides) such as polyacrylamide per se, poly(methacrylamide), poly(dimethylacrylamide), and poly(N-isopropylacrylamide); poly(olefinic alcohol)s such as poly(vinyl alcohol); poly(N-vinyl lactams) such as poly(vinyl pyrroli-

done), poly(N-vinyl caprolactam), and copolymers thereof; polyoxazolines, including poly(methyloxazoline) and poly(ethyloxazoline); and polyvinylamines. It must be emphasized that the aforementioned list of polymers is not exhaustive, and a variety of other synthetic hydrophilic polymers may be used, as will be appreciated by those skilled in the art.

[0672] The synthetic crosslinkable hydrophilic polymer may be a homopolymer, a block copolymer, a random copolymer, or a graft copolymer. In addition, the polymer may be linear or branched, and if branched, may be minimally to highly branched, dendrimeric, hyperbranched, or a star polymer. The polymer may include biodegradable segments and blocks, either distributed throughout the polymer's molecular structure or present as a single block, as in a block copolymer. Biodegradable segments are those that degrade so as to break covalent bonds. Typically, biodegradable segments are segments that are hydrolyzed in the presence of water and/or enzymatically cleaved in situ. Biodegradable segments may be composed of small molecular segments such as ester linkages, anhydride linkages, ortho ester linkages, ortho carbonate linkages, amide linkages, phosphonate linkages, etc. Larger biodegradable "blocks" will generally be composed of oligomeric or polymeric segments incorporated within the hydrophilic polymer. Illustrative oligomeric and polymeric segments that are biodegradable include, by way of example, poly(amino acid) segments, poly(orthoester) segments, poly(orthocarbonate) segments, and the like.

[0673] Other suitable synthetic crosslinkable hydrophilic polymers include chemically synthesized polypeptides, particularly polynucleophilic polypeptides that have been synthesized to incorporate amino acids containing primary amino groups (such as lysine) and/or amino acids containing thiol groups (such as cysteine). Poly(lysine), a synthetically produced polymer of the amino acid lysine (145 MW), is particularly preferred. Poly(lysine)s have been prepared having anywhere from 6 to about 4,000 primary amino groups, corresponding to molecular weights of about 870 to about 580,000. Poly(lysine)s for use in the present invention preferably have a molecular weight within the range of about 1,000 to about 300,000, more preferably within the range of about 5,000 to about 100,000, and most preferably, within the range of about 8,000 to about 15,000. Poly(lysine)s of varying molecular weights are commercially available from Peninsula Laboratories, Inc. (Belmont, Calif.).

[0674] The synthetic crosslinkable hydrophilic polymer may be a homopolymer, a block copolymer, a random copolymer, or a graft copolymer. In addition, the polymer may be linear or branched, and if branched, may be minimally to highly branched, dendrimeric, hyperbranched, or a star polymer. The polymer may include biodegradable segments and blocks, either distributed throughout the polymer's molecular structure or present as a single block, as in a block copolymer. Biodegradable segments are those that degrade so as to break covalent bonds. Typically, biodegradable segments are segments that are hydrolyzed in the presence of water and/or enzymatically cleaved in situ. Biodegradable segments may be composed of small molecular segments such as ester linkages, anhydride linkages, ortho ester linkages, ortho carbonate linkages, amide linkages, phosphonate linkages, etc. Larger biodegradable "blocks" will generally be composed of oligomeric or polymeric segments incorporated within the hydrophilic polymer. Illustrative oligomeric and polymeric segments that are biodegradable include, by way of example, poly(amino acid) segments, poly(orthoester) segments, poly(orthocarbonate) segments, and the like.

[0675] Although a variety of different synthetic crosslinkable hydrophilic polymers can be used in the present compositions, as indicated above, preferred synthetic crosslinkable hydrophilic polymers are polyethylene glycol (PEG) and polyglycerol (PG), particularly highly branched polyglycerol. Various forms of PEG are extensively used in the modification of biologically active molecules because PEG lacks toxicity, antigenicity, and immunogenicity (i.e., is biocompatible), can be formulated so as to have a wide range of solubilities, and do not typically interfere with the enzymatic activities and/or conformations of peptides. A particularly preferred synthetic crosslinkable hydrophilic polymer for certain applications is a polyethylene glycol (PEG) having a molecular weight within the range of about 100 to about 100,000 mol. wt., although for highly branched PEG, far higher molecular weight polymers can be employed—up to 1,000,000 or more—providing that biodegradable sites are incorporated ensuring that all degradation products will have a molecular weight of less than about 30,000. For most PEGs, however, the preferred molecular weight is about 1,000 to about 20,000 mol. wt., more preferably within the range of about 7,500 to about 20,000 mol. wt. Most preferably, the polyethylene glycol has a molecular weight of approximately 10,000 mol. wt.

[0676] Naturally occurring crosslinkable hydrophilic polymers include, but are not limited to: proteins such as collagen, fibronectin, albumins, globulins, fibrinogen, and fibrin, with collagen particularly preferred; carboxylated polysaccharides such as polymannuronic acid and polygalacturonic acid; aminated polysaccharides, particularly the glycosaminoglycans, e.g., hyaluronic acid, chitin, chondroitin sulfate A, B, or C, keratin sulfate, keratosulfate and heparin; and activated polysaccharides such as dextran and starch derivatives. Collagen and glycosaminoglycans are examples of naturally occurring hydrophilic polymers for use herein, with methylated collagen being a preferred hydrophilic polymer.

[0677] Any of the hydrophilic polymers herein must contain, or be activated to contain, functional groups, i.e., nucleophilic or electrophilic groups, which enable crosslinking. Activation of PEG is discussed below; it is to be understood, however, that the following discussion is for purposes of illustration and analogous techniques may be employed with other polymers.

[0678] With respect to PEG, first of all, various functionalized polyethylene glycols have been used effectively in fields such as protein modification (see Abuchowski et al., Enzymes as Drugs, John Wiley & Sons: New York, N.Y. (1981) pp. 367-383; and Dreborg et al., *Crit. Rev. Therap. Drug Carrier Syst.* (1990) 6:315), peptide chemistry (see Mutter et al., The Peptides, Academic: New York, N.Y. 2:285-332; and Zalipsky et al., *Int. J. Peptide Protein Res.* (1987) 30:740), and the synthesis of polymeric drugs (see Zalipsky et al., *Eur. Polym. J.* (1983) 19:1177; and Ouchi et al., *J. Macromol. Sci. Chem.* (1987) A24:1011).

[0679] Activated forms of PEG, including multifunctionally activated PEG, are commercially available, and are also

easily prepared using known methods. For example, see Chapter 22 of Poly(ethylene Glycol) Chemistry: Biotechnical and Biomedical Applications, J. Milton Harris, ed., Plenum Press, NY (1992); and Shearwater Polymers, Inc. Catalog, Polyethylene Glycol Derivatives, Huntsville, Ala. (1997-1998).

[0680] Structures for some specific, tetrafunctionally activated forms of PEG are shown in FIGS. 1 to 10 of U.S. Pat. No. 5,874,500, as are generalized reaction products obtained by reacting the activated PEGs with multi-amino PEGs, i.e., a PEG with two or more primary amino groups. The activated PEGs illustrated have a pentaerythritol (2,2-bis(hydroxymethyl)-1,3-propanediol) core. Such activated PEGs, as will be appreciated by those in the art, are readily prepared by conversion of the exposed hydroxyl groups in the PEGylated polyol (i.e., the terminal hydroxyl groups on the PEG chains) to carboxylic acid groups (typically by reaction with an anhydride in the presence of a nitrogenous base), followed by esterification with N-hydroxysuccinimide, N-hydroxysulfosuccinimide, or the like, to give the polyfunctionally activated PEG.

[0681] Hydrophobic Polymers:

[0682] The crosslinkable compositions of the invention can also include hydrophobic polymers, although for most uses hydrophilic polymers are preferred. Polylactic acid and polyglycolic acid are examples of two hydrophobic polymers that can be used. With other hydrophobic polymers, only short-chain oligomers should be used, containing at most about 14 carbon atoms, to avoid solubility-related problems during reaction.

[0683] Low Molecular Weight Components:

[0684] As indicated above, the molecular core of one or more of the crosslinkable components can also be a low molecular weight compound, i.e., a C_2-C_{14} hydrocarbyl group containing zero to 2 heteroatoms selected from N, O, S and combinations thereof. Such a molecular core can be substituted with nucleophilic groups or with electrophilic groups.

[0685] When the low molecular weight molecular core is substituted with primary amino groups, the component may be, for example, ethylenediamine (H_2N—CH_2CH_2—NH_2), tetramethylenediamine (H_2N—(CH_4)—NH_2), pentamethylenediamine (cadaverine) (H_2N—(CH_5)—NH_2), hexamethylenediamine (H_2N—(CH_6)—NH_2), bis(2-aminoethyl)amine (H_2N-[CH_2CH_2—$NH_2]_2$), or tris(2-aminoethyl)amine (N—[CH_2CH_2—$NH_2]_3$).

[0686] Low molecular weight diols and polyols include trimethylolpropane, di(trimethylol propane), pentaerythritol, and diglycerol, all of which require activation with a base in order to facilitate their reaction as nucleophiles. Such diols and polyols may also be functionalized to provide di- and poly-carboxylic acids, functional groups that are, as noted earlier herein, also useful as nucleophiles under certain conditions. Polyacids for use in the present compositions include, without limitation, trimethylolpropane-based tricarboxylic acid, di(trimethylol propane)-based tetracarboxylic acid, heptanedioic acid, octanedioic acid (suberic acid), and hexadecanedioic acid (thapsic acid), all of which are commercially available and/or readily synthesized using known techniques.

[0687] Low molecular weight di- and poly-electrophiles include, for example, disuccinimidyl suberate (DSS), bis-(sulfosuccinimidyl) suberate (BS_3), dithiobis(succinimidyl-propionate) (DSP), bis(2-succinimidooxycarbonyloxy) ethyl sulfone (BSOCOES), and 3,3'-dithiobis(sulfosuccinimidylpropionate (DTSPP), and their analogs and derivatives. The aforementioned compounds are commercially available from Pierce (Rockford, Ill.). Such di- and poly-electrophiles can also be synthesized from di- and polyacids, for example by reaction with an appropriate molar amount of N-hydroxysuccinimide in the presence of DCC. Polyols such as trimethylolpropane and di(trimethylol propane) can be converted to carboxylic acid form using various known techniques, then further derivatized by reaction with NHS in the presence of DCC to produce trifunctionally and tetrafunctionally activated polymers.

[0688] Delivery Systems:

[0689] Suitable delivery systems for the homogeneous dry powder composition (containing at least two crosslinkable polymers) and the two buffer solutions may involve a multi-compartment spray device, where one or more compartments contains the powder and one or more compartments contain the buffer solutions needed to provide for the aqueous environment, so that the composition is exposed to the aqueous environment as it leaves the compartment. Many devices that are adapted for delivery of multi-component tissue sealants/hemostatic agents are well known in the art and can also be used in the practice of the present invention. Alternatively, the composition can be delivered using any type of controllable extrusion system, or it can be delivered manually in the form of a dry powder, and exposed to the aqueous environment at the site of administration.

[0690] The homogeneous dry powder composition and the two buffer solutions may be conveniently formed under aseptic conditions by placing each of the three ingredients (dry powder, acidic buffer solution and basic buffer solution) into separate syringe barrels. For example, the composition, first buffer solution and second buffer solution can be housed separately in a multiple-compartment syringe system having a multiple barrels, a mixing head, and an exit orifice. The first buffer solution can be added to the barrel housing the composition to dissolve the composition and form a homogeneous solution, which is then extruded into the mixing head. The second buffer solution can be simultaneously extruded into the mixing head. Finally, the resulting composition can then be extruded through the orifice onto a surface.

[0691] For example, the syringe barrels holding the dry powder and the basic buffer may be part of a dual-syringe system, e.g., a double barrel syringe as described in U.S. Pat. No. 4,359,049 to RedI et al. In this embodiment, the acid buffer can be added to the syringe barrel that also holds the dry powder, so as to produce the homogeneous solution. In other words, the acid buffer may be added (e.g., injected) into the syringe barrel holding the dry powder to thereby produce a homogeneous solution of the first and second components. This homogeneous solution can then be extruded into a mixing head, while the basic buffer is simultaneously extruded into the mixing head. Within the mixing head, the homogeneous solution and the basic buffer are mixed together to thereby form a reactive mixture. Thereafter, the reactive mixture is extruded through an

orifice and onto a surface (e.g., tissue), where a film is formed, which can function as a sealant or a barrier, or the like. The reactive mixture begins forming a three-dimensional matrix immediately upon being formed by the mixing of the homogeneous solution and the basic buffer in the mixing head. Accordingly, the reactive mixture is preferably extruded from the mixing head onto the tissue very quickly after it is formed so that the three-dimensional matrix forms on, and is able to adhere to, the tissue.

[0692] Other systems for combining two reactive liquids are well known in the art, and include the systems described in U.S. Pat. No. 6,454,786 to Holm et al.; U.S. Pat. No. 6,461,325 to Delmotte et al.; U.S. Pat. No. 5,585,007 to Antanavich et al.; U.S. Pat. No. 5,116,315 to Capozzi et al.; and U.S. Pat. No. 4,631,055 to Redl et al.

[0693] Storage and Handling:

[0694] Because crosslinkable components containing electrophilic groups react with water, the electrophilic component or components are generally stored and used in sterile, dry form to prevent hydrolysis. Processes for preparing synthetic hydrophilic polymers containing multiple electrophilic groups in sterile, dry form are set forth in commonly assigned U.S. Pat. No. 5,643,464 to Rhee et al. For example, the dry synthetic polymer may be compression molded into a thin sheet or membrane, which can then be sterilized using gamma or, preferably, e-beam irradiation. The resulting dry membrane or sheet can be cut to the desired size or chopped into smaller size particulates.

[0695] Components containing multiple nucleophilic groups are generally not water-reactive and can therefore be stored either dry or in aqueous solution. If stored as a dry, particulate, solid, the various components of the crosslinkable composition may be blended and stored in a single container. Admixture of all components with water, saline, or other aqueous media should not occur until immediately prior to use.

[0696] In an alternative embodiment, the crosslinking components can be mixed together in a single aqueous medium in which they are both unreactive, i.e., such as in a low pH buffer. Thereafter, they can be sprayed onto the targeted tissue site along with a high pH buffer, after which they will rapidly react and form a gel.

[0697] Suitable liquid media for storage of crosslinkable compositions include aqueous buffer solutions such as monobasic sodium phosphate/dibasic sodium phosphate, sodium carbonate/sodium bicarbonate, glutamate or acetate, at a concentration of 0.5 to 300 mM. In general, a sulfhydryl-reactive component such as PEG substituted with maleimido groups or succinimidyl esters is prepared in water or a dilute buffer, with a pH of between around 5 to 6. Buffers with pKs between about 8 and 10.5 for preparing a polysulfhydryl component such as sulfhydryl-PEG are useful to achieve fast gelation time of compositions containing mixtures of sulfhydryl-PEG and SG-PEG. These include carbonate, borate and AMPSO (3-[(1,1-dimethyl-2-hydroxyethyl)amino]2-hydroxy-propane-sulfonic acid). In contrast, using a combination of maleimidyl PEG and sulfhydryl-PEG, a pH of around 5 to 9 is preferred for the liquid medium used to prepare the sulfhydryl PEG.

[0698] Collagen+Fibrinogen and/or Thrombin (e.g., Costasis)

[0699] In yet another aspect, the polymer composition may include collagen in combination with fibrinogen and/or thrombin. (See, e.g., U.S. Pat. Nos. 5,290,552; 6,096,309; and 5,997,811). For example, an aqueous composition may include a fibrinogen and FXIII, particularly plasma, collagen in an amount sufficient to thicken the composition, thrombin in an amount sufficient to catalyze polymerization of fibrinogen present in the composition, and Ca^{2+} and, optionally, an antifibrinolytic agent in amount sufficient to retard degradation of the resulting adhesive clot. The composition may be formulated as a two-part composition that may be mixed together just prior to use, in which fibrinogen/FXIII and collagen constitute the first component, and thrombin together with an antifibrinolytic agent, and Ca^{2+} constitute the second component.

[0700] Plasma, which provides a source of fibrinogen, may be obtained from the patient for which the composition is to be delivered. The plasma can be used "as is" after standard preparation which includes centrifuging out cellular components of blood. Alternatively, the plasma can be further processed to concentrate the fibrinogen to prepare a plasma cryoprecipitate. The plasma cryoprecipitate can be prepared by freezing the plasma for at least about an hour at about −20° C., and then storing the frozen plasma overnight at about 4° C. to slowly thaw. The thawed plasma is centrifuged and the plasma cryoprecipitate is harvested by removing approximately four-fifths of the plasma to provide a cryoprecipitate comprising the remaining one-fifth of the plasma. Other fibrinogen/FXIII preparations may be used, such as cryoprecipitate, patient autologous fibrin sealant, fibrinogen analogs or other single donor or commercial fibrin sealant materials. Approximately 0.5 ml to about 1.0 ml of either the plasma or the plasma-cryoprecipitate provides about 1 to 2 ml of adhesive composition which is sufficient for use in middle ear surgery. Other plasma proteins (e.g., albumin, plasminogen, von Willebrands factor, Factor VIII, etc.) may or may not be present in the fibrinogen/FXII separation due to wide variations in the formulations and methods to derive them.

[0701] Collagen, preferably hypoallergenic collagen, is present in the composition in an amount sufficient to thicken the composition and augment the cohesive properties of the preparation. The collagen may be atelopeptide collagen or telopeptide collagen, e.g., native collagen. In addition to thickening the composition, the collagen augments the fibrin by acting as a macromolecular lattice work or scaffold to which the fibrin network adsorbs. This gives more strength and durability to the resulting glue clot with a relatively low concentration of fibrinogen in comparison to the various concentrated autogenous fibrinogen glue formulations (i.e., AFGs).

[0702] The form of collagen which is employed may be described as at least "near native" in its structural characteristics. It may be further characterized as resulting in insoluble fibers at a pH above 5; unless crosslinked or as part of a complex composition, e.g., bone, it will generally consist of a minor amount by weight of fibers with diameters greater than 50 nm, usually from about 1 to 25 volume % and there will be substantially little, if any, change in the

helical structure of the fibrils. In addition, the collagen composition must be able to enhance gelation in the surgical adhesion composition.

[0703] A number of commercially available collagen preparations may be used. ZYDERM Collagen Implant (ZCI) has a fibrillar diameter distribution consisting of 5 to 10 nm diameter fibers at 90% volume content and the remaining 10% with greater than about 50 nm diameter fibers. ZCI is available as a fibrillar slurry and solution in phosphate buffered isotonic saline, pH 7.2, and is injectable with fine gauge needles. As distinct from ZCI, cross-linked collagen available as ZYPLAST may be employed. ZYPLAST is essentially an exogenously crosslinked (glutaraldehyde) version of ZCI. The material has a somewhat higher content of greater than about 50 nm diameter fibrils and remains insoluble over a wide pH range. Crosslinking has the effect of mimicking in vivo endogenous crosslinking found in many tissues.

[0704] Thrombin acts as a catalyst for fibrinogen to provide fibrin, an insoluble polymer and is present in the composition in an amount sufficient to catalyze polymerization of fibrinogen present in the patient plasma. Thrombin also activates FXIII, a plasma protein that catalyzes covalent crosslinks in fibrin, rendering the resultant clot insoluble. Usually the thrombin is present in the adhesive composition in concentration of from about 0.01 to about 1000 or greater NIH units (NIHu) of activity, usually about i to about 500 NIHu, most usually about 200 to about 500 NIHu. The thrombin can be from a variety of host animal sources, conveniently bovine. Thrombin is commercially available from a variety of sources including Parke-Davis, usually lyophilized with buffer salts and stabilizers in vials which provide thrombin activity ranging from about 1000 NIHu to 10,000 NIHu. The thrombin is usually prepared by reconstituting the powder by the addition of either sterile distilled water or isotonic saline. Alternately, thrombin analogs or reptile-sourced coagulants may be used.

[0705] The composition may additionally comprise an effective amount of an antifibrinolytic agent to enhance the integrity of the glue clot as the healing processes occur. A number of antifibrinolytic agents are well known and include aprotinin, C1-esterase inhibitor and ϵ-amino-n-caproic acid (EACA). ϵ-amino-n-caproic acid, the only antifibrinolytic agent approved by the FDA, is effective at a concentration of from about 5 mg/ml to about 40 mg/ml of the final adhesive composition, more usually from about 20 to about 30 mg/ml. EACA is commercially available as a solution having a concentration of about 250 mg/ml. Conveniently, the commercial solution is diluted with distilled water to provide a solution of the desired concentration. That solution is desirably used to reconstitute lyophilized thrombin to the desired thrombin concentration.

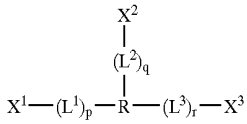
[0706] Other examples of in situ forming materials based on the crosslinking of proteins are described, e.g., in U.S. Pat. Nos. RE38158; 4,839,345; 5,514,379, 5,583,114; 6,458,147; 6,371,975; 5,290,552; 6,096,309; U.S. Patent Application Publication Nos. 2002/0161399; 2001/0018598 and PCT Publication Nos. WO 03/090683; WO 01/45761; WO 99/66964 and WO 96/03159).

[0707] Self-Reactive Compounds

[0708] In one aspect, the therapeutic agent is released from a crosslinked matrix formed, at least in part, from a self-reactive compound. As used herein, a self-reactive compound comprises a core substituted with a minimum of three reactive groups. The reactive groups may be directed attached to the core of the compound, or the reactive groups may be indirectly attached to the compound's core, e.g., the reactive groups are joined to the core through one or more linking groups.

[0709] Each of the three reactive groups that are necessarily present in a self-reactive compound can undergo a bond-forming reaction with at least one of the remaining two reactive groups. For clarity it is mentioned that when these compounds react to form a crosslinked matrix, it will most often happen that reactive groups on one compound will reactive with reactive groups on another compound. That is, the term "self-reactive" is not intended to mean that each self-reactive compound necessarily reacts with itself, but rather that when a plurality of identical self-reactive compounds are in combination and undergo a crosslinking reaction, then these compounds will react with one another to form the matrix. The compounds are "self-reactive" in the sense that they can react with other compounds having the identical chemical structure as themselves.

[0710] The self-reactive compound comprises at least four components: a core and three reactive groups. In one embodiment, the self-reactive compound can be characterized by the formula (I), where R is the core, the reactive groups are represented by X^1, X^2 and X^3, and a linker (L) is optionally present between the core and a functional group.


(1)

[0711] The core R is a polyvalent moiety having attachment to at least three groups (i.e., it is at least trivalent) and may be, or may contain, for example, a hydrophilic polymer, a hydrophobic polymer, an amphiphilic polymer, a C_{2-14} hydrocarbyl, or a C_{2-14} hydrocarbyl which is heteroatom-containing. The linking groups L^1, L^2, and L^3 may be the same or different. The designators p, q and r are either 0 (when no linker is present) or 1 (when a linker is present). The reactive groups X^1, X^2 and X^3 may be the same or different. Each of these reactive groups reacts with at least one other reactive group to form a three-dimensional matrix. Therefore X^1 can react with X^2 and/or X^3, X^2 can react with X^1 and/or X^3, X^3 can react with X^1 and/or X^2 and so forth. A trivalent core will be directly or indirectly bonded to three functional groups, a tetravalent core will be directly or indirectly bonded to four functional groups, etc.

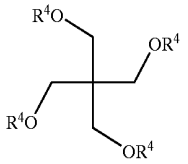
[0712] Each side chain typically has one reactive group. However, the invention also encompasses self-reactive compounds where the side chains contain more than one reactive group. Thus, in another embodiment of the invention, the self-reactive compound has the formula (II):

$$[X'\text{-}(L^4)_a\text{-}Y'\text{-}(L^5)_b]_c\text{-}R'$$

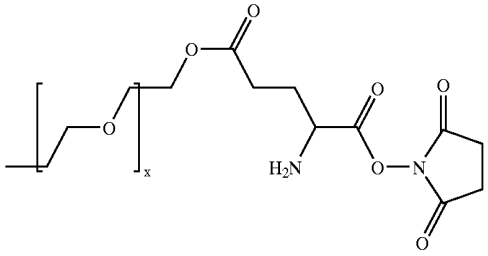
[0713] where: a and b are integers from 0-1; c is an integer from 3-12; R' is selected from hydrophilic polymers, hydrophobic polymers, amphiphilic polymers, C_{2-14} hydrocarbyls,

and heteroatom-containing C_{2-14} hydrocarbyls; X' and Y' are reactive groups and can be the same or different; and L^4 and L^5 are linking groups. Each reactive group inter-reacts with the other reactive group to form a three-dimensional matrix. The compound is essentially non-reactive in an initial environment but is rendered reactive upon exposure to a modification in the initial environment that provides a modified environment such that a plurality of the self-reactive compounds inter-react in the modified environment to form a three-dimensional matrix. In one preferred embodiment, R is a hydrophilic polymer. In another preferred embodiment, X' is a nucleophilic group and Y' is an electrophilic group.

[0714] The following self-reactive compound is one example of a compound of formula (II):

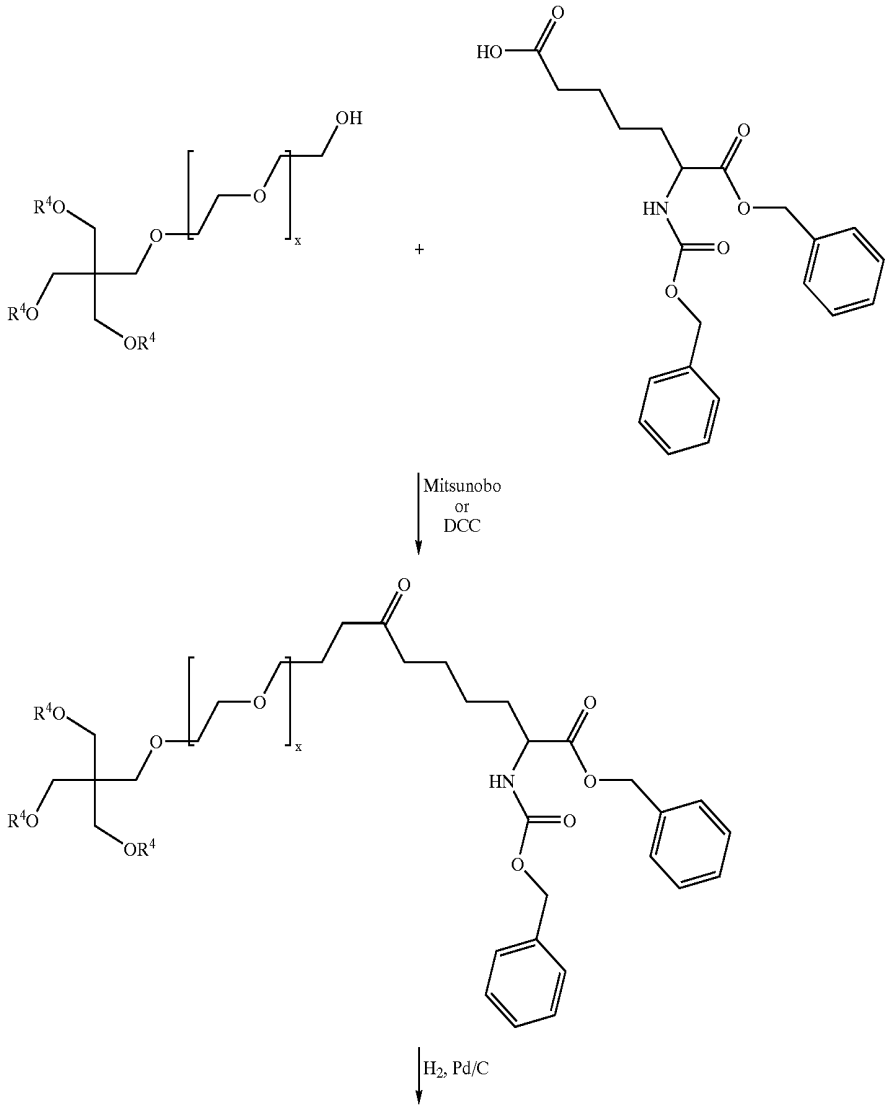


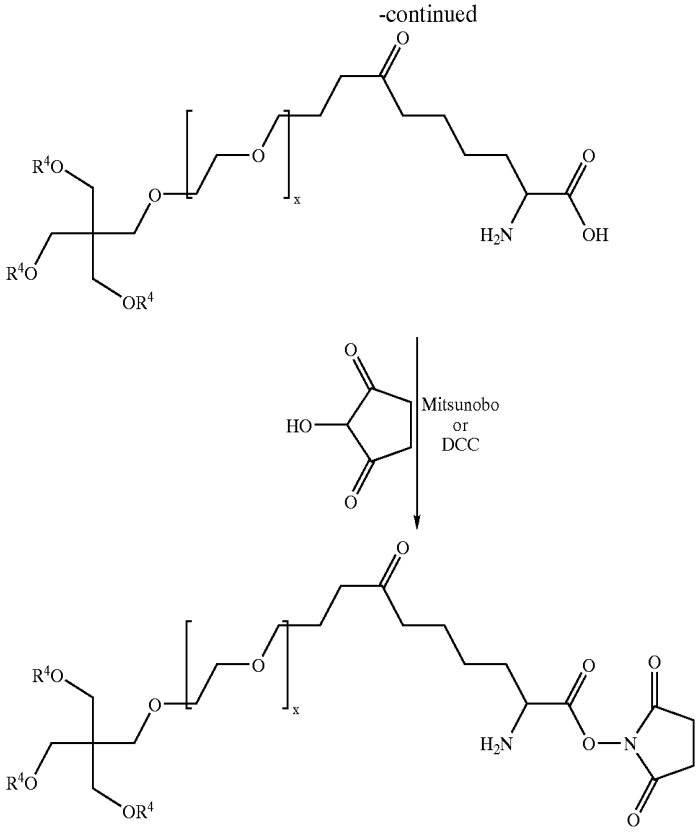
[0715] where R^4 has the formula:



[0716] Thus, in formula (II), a and b are 1; c is 4; the core R' is the hydrophilic polymer, tetrafunctionally activated polyethylene glycol, $(C(CH_2—O—)_4$; X' is the electrophilic reactive group, succinimidyl; Y' is the nucleophilic reactive group —CH—NH_2; L^4 is —C(O)—O—; and L^5 is —$(CH_2—CH_2—O—CH_2)_x—CH_2—O—C(O)—(CH_2)_2$—.

[0717] The self-reactive compounds of the invention are readily synthesized by techniques that are well known in the art. An exemplary synthesis is set forth below:





[0718] The reactive groups are selected so that the compound is essentially non-reactive in an initial environment. Upon exposure to a specific modification in the initial environment, providing a modified environment, the compound is rendered reactive and a plurality of self-reactive compounds are then able to inter-react in the modified environment to form a three-dimensional matrix. Examples of modification in the initial environment are detailed below, but include the addition of an aqueous medium, a change in pH, exposure to ultraviolet radiation, a change in temperature, or contact with a redox initiator.

[0719] The core and reactive groups can also be selected so as to provide a compound that has one of more of the following features: are biocompatible, are non-immunogenic, and do not leave any toxic, inflammatory or immunogenic reaction products at the site of administration. Similarly, the core and reactive groups can also be selected so as to provide a resulting matrix that has one or more of these features.

[0720] In one embodiment of the invention, substantially immediately or immediately upon exposure to the modified environment, the self-reactive compounds inter-react form a three-dimensional matrix. The term "substantially immediately" is intended to mean within less than five minutes, preferably within less than two minutes, and the term "immediately" is intended to mean within less than one minute, preferably within less than 30 seconds.

[0721] In one embodiment, the self-reactive compound and resulting matrix are not subject to enzymatic cleavage by matrix metalloproteinases such as collagenase, and are therefore not readily degradable in vivo. Further, the self-reactive compound may be readily tailored, in terms of the selection and quantity of each component, to enhance certain properties, e.g., compression strength, swellability, tack, hydrophilicity, optical clarity, and the like.

[0722] In one preferred embodiment, R is a hydrophilic polymer. In another preferred embodiment, X is a nucleophilic group, Y is an electrophilic group and Z is either an electrophilic or a nucleophilic group. Additional embodiments are detailed below.

[0723] A higher degree of inter-reaction, e.g., crosslinking, may be useful when a less swellable matrix is desired or increased compressive strength is desired. In those embodiments, it may be desirable to have n be an integer from 2-12. In addition, when a plurality of self-reactive compounds are utilized, the compounds may be the same or different.

[0724] E. Reactive Groups

[0725] Prior to use, the self-reactive compound is stored in an initial environment that insures that the compound remain essentially non-reactive until use. Upon modification of this environment, the compound is rendered reactive and a plurality of compounds will then inter-react to form the desired matrix. The initial environment, as well as the modified environment, is thus determined by the nature of the reactive groups involved.

[0726] The number of reactive groups can be the same or different. However, in one embodiment of the invention, the number of reactive groups is approximately equal. As used

in this context, the term "approximately" refers to a 2:1 to 1:2 ratio of moles of one reactive group to moles of a different reactive groups. A 1:1:1 molar ratio of reactive groups is generally preferred.

[0727] In general, the concentration of the self-reactive compounds in the modified environment, when liquid in nature, will be in the range of about 1 to 50 wt %, generally about 2 to 40 wt %. The preferred concentration of the compound in the liquid will depend on a number of factors, including the type of compound (i.e., type of molecular core and reactive groups), its molecular weight, and the end use of the resulting three-dimensional matrix. For example, use of higher concentrations of the compounds, or using highly functionalized compounds, will result in the formation of a more tightly crosslinked network, producing a stiffer, more robust gel. As such, compositions intended for use in tissue augmentation will generally employ concentrations of self-reactive compounds that fall toward the higher end of the preferred concentration range. Compositions intended for use as bioadhesives or in adhesion prevention do not need to be as firm and may therefore contain lower concentrations of the self-reactive compounds.

[0728] 1) Electrophilic and Nucleophilic Reactive Groups

[0729] In one embodiment of the invention, the reactive groups are electrophilic and nucleophilic groups, which undergo a nucleophilic substitution reaction, a nucleophilic addition reaction, or both. The term "electrophilic" refers to a reactive group that is susceptible to nucleophilic attack, i.e., susceptible to reaction with an incoming nucleophilic group. Electrophilic groups herein are positively charged or electron-deficient, typically electron-deficient. The term "nucleophilic" refers to a reactive group that is electron rich, has an unshared pair of electrons acting as a reactive site, and reacts with a positively charged or electron-deficient site. For such reactive groups, the modification in the initial environment comprises the addition of an aqueous medium and/or a change in pH.

[0730] In one embodiment of the invention, X1 (also referred to herein as X) can be a nucleophilic group and X2 (also referred to herein as Y) can be an electrophilic group or vice versa, and X3 (also referred to herein as Z) can be either an electrophilic or a nucleophilic group.

[0731] X may be virtually any nucleophilic group, so long as reaction can occur with the electrophilic group Y and also with Z, when Z is electrophilic (ZEL). Analogously, Y may be virtually any electrophilic group, so long as reaction can take place with X and also with Z when Z is nucleophilic (Z_{NU}). The only limitation is a practical one, in that reaction between X and Y, and X and Z_{EL}, or Y and Z_{NU} should be fairly rapid and take place automatically upon admixture with an aqueous medium, without need for heat or potentially toxic or non-biodegradable reaction catalysts or other chemical reagents. It is also preferred although not essential that reaction occur without need for ultraviolet or other radiation. In one embodiment, the reactions between X and Y, and between either X and Z_{EL} or Y and Z_{NU}, are complete in under 60 minutes, preferably under 30 minutes. Most preferably, the reaction occurs in about 5 to 15 minutes or less.

[0732] Examples of nucleophilic groups suitable as X or Fn_{NU} include, but are not limited to: —NH_2, —NHR^1, —$N(R^1)_2$, —SH, —OH, —COOH, —C_6H_4—OH, —H, —PH_2, —PHR^1, —$P(R^1)_2$, —NH—NH_2, —CO—NH—NH_2, —C_5H_4N, etc. wherein R^1 is a hydrocarbyl group and each R_1 may be the same or different. R^1 is typically alkyl or monocyclic aryl, preferably alkyl, and most preferably lower alkyl. Organometallic moieties are also useful nucleophilic groups for the purposes of the invention, particularly those that act as carbanion donors. Examples of organometallic moieties include: Grignard functionalities —R^2MgHal wherein R^2 is a carbon atom (substituted or unsubstituted), and Hal is halo, typically bromo, iodo or chloro, preferably bromo; and lithium-containing functionalities, typically alkyllithium groups; sodium-containing functionalities.

[0733] It will be appreciated by those of ordinary skill in the art that certain nucleophilic groups must be activated with a base so as to be capable of reaction with an electrophilic group. For example, when there are nucleophilic sulfhydryl and hydroxyl groups in the self-reactive compound, the compound must be admixed with an aqueous base in order to remove a proton and provide an —S^- or —O^- species to enable reaction with the electrophilic group. Unless it is desirable for the base to participate in the reaction, a non-nucleophilic base is preferred. In some embodiments, the base may be present as a component of a buffer solution. Suitable bases and corresponding crosslinking reactions are described herein.

[0734] The selection of electrophilic groups provided on the self-reactive compound, must be made so that reaction is possible with the specific nucleophilic groups. Thus, when the X reactive groups are amino groups, the Y and any ZEL groups are selected so as to react with amino groups. Analogously, when the X reactive groups are sulfhydryl moieties, the corresponding electrophilic groups are sulfhydryl-reactive groups, and the like. In general, examples of electrophilic groups suitable as Y or ZEL include, but are not limited to, —CO—Cl, —(CO)—O—(CO)—R (where R is an alkyl group), —CH═CH—CH═O and —CH═CH—$C(CH_3)$═O, halo, —N═C═O, —N═C═S, —SO_2CH═CH_2, —O(CO)—C═CH_2, —O(CO)—$C(CH_3)$═CH_2, —S—S—(C_5H_4N), —O(CO)—$C(CH_2CH_3)$═CH_2, —CH═CH—C═NH, —COOH, —(CO)O—$N(COCH_2)_2$, —CHO, —(CO)O—$N(COCH_2)_2$—$S(O)_2OH$, and —$N(COCH)_2$.

[0735] When X is amino (generally although not necessarily primary amino), the electrophilic groups present on Y and ZEL are amine-reactive groups. Exemplary amine-reactive groups include, by way of example and not limitation, the following groups, or radicals thereof: (1) carboxylic acid esters, including cyclic esters and "activated" esters; (2) acid chloride groups (—CO—Cl); (3) anhydrides (—(CO)—O—(CO)—R, where R is an alkyl group); (4) ketones and aldehydes, including α,β-unsaturated aldehydes and ketones such as —CH═CH—CH═O and —CH═CH—$C(CH_3)$═O; (5) halo groups; (6) isocyanate group (—N═C═O); (7) thioisocyanato group (—N═C═S); (8) epoxides; (9) activated hydroxyl groups (e.g., activated with conventional activating agents such as carbonyldiimidazole or sulfonyl chloride); and (10) olefins, including conjugated olefins, such as ethenesulfonyl (—SO_2CH═CH_2) and analogous functional groups, including acrylate (—O(CO)—C═CH_2), methacrylate

(—O(CO)—C(CH_3)=CH_2), ethyl acrylate (—O(CO)—C(CH_2CH_3)=CH_2), and ethyleneimino (—CH=CH—C=NH).

[0736] In one embodiment the amine-reactive groups contain an electrophilically reactive carbonyl group susceptible to nucleophilic attack by a primary or secondary amine, for example the carboxylic acid esters and aldehydes noted above, as well as carboxyl groups (—COOH).

[0737] Since a carboxylic acid group per se is not susceptible to reaction with a nucleophilic amine, components containing carboxylic acid groups must be activated so as to be amine-reactive. Activation may be accomplished in a variety of ways, but often involves reaction with a suitable hydroxyl-containing compound in the presence of a dehydrating agent such as dicyclohexylcarbodiimide (DCC) or dicyclohexylurea (DHU). For example, a carboxylic acid can be reacted with an alkoxy-substituted N-hydroxy-succinimide or N-hydroxysulfosuccinimide in the presence of DCC to form reactive electrophilic groups, the N-hydroxysuccinimide ester and the N-hydroxysulfosuccinimide ester, respectively. Carboxylic acids may also be activated by reaction with an acyl halide such as an acyl chloride (e.g., acetyl chloride), to provide a reactive anhydride group. In a further example, a carboxylic acid may be converted to an acid chloride group using, e.g., thionyl chloride or an acyl chloride capable of an exchange reaction. Specific reagents and procedures used to carry out such activation reactions will be known to those of ordinary skill in the art and are described in the pertinent texts and literature.

[0738] Accordingly, in one embodiment, the amine-reactive groups are selected from succinimidyl ester (—O(CO)—N($COCH_2$)$_2$), sulfosuccinimidyl ester (—O(CO)—N($COCH_2$)$_2$—S(O)$_2$OH), maleimido (—N($COCH$)$_2$), epoxy, isocyanato, thioisocyanato, and ethenesulfonyl.

[0739] Analogously, when X is sulfhydryl, the electrophilic groups present on Y and ZEL are groups that react with a sulfhydryl moiety. Such reactive groups include those that form thioester linkages upon reaction with a sulfhydryl group, such as those described in WO 00/62827 to Wallace et al. As explained in detail therein, sulfhydryl reactive groups include, but are not limited to: mixed anhydrides; ester derivatives of phosphorus; ester derivatives of p-nitrophenol, p-nitrothiophenol and pentafluorophenol; esters of substituted hydroxylamines, including N-hydroxyphthalimide esters, N-hydroxysuccinimide esters, N-hydroxysulfosuccinimide esters, and N-hydroxyglutarimide esters; esters of 1-hydroxybenzotriazole; 3-hydroxy-3,4-dihydro-benzotriazin-4-one; 3-hydroxy-3,4-dihydro-quinazoline-4-one; carbonylimidazole derivatives; acid chlorides; ketenes; and isocyanates. With these sulfhydryl reactive groups, auxiliary reagents can also be used to facilitate bond formation, e.g., 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide can be used to facilitate coupling of sulfhydryl groups to carboxyl-containing groups.

[0740] In addition to the sulfhydryl reactive groups that form thioester linkages, various other sulfhydryl reactive functionalities can be utilized that form other types of linkages. For example, compounds that contain methyl imidate derivatives form imido-thioester linkages with sulfhydryl groups. Alternatively, sulfhydryl reactive groups can be employed that form disulfide bonds with sulfhydryl groups; such groups generally have the structure —S—S—Ar where Ar is a substituted or unsubstituted nitrogen-containing heteroaromatic moiety or a non-heterocyclic aromatic group substituted with an electron-withdrawing moiety, such that Ar may be, for example, 4-pyridinyl, o-nitrophenyl, m-nitrophenyl, p-nitrophenyl, 2,4-dinitrophenyl, 2-nitro-4-benzoic acid, 2-nitro-4-pyridinyl, etc. In such instances, auxiliary reagents, i.e., mild oxidizing agents such as hydrogen peroxide, can be used to facilitate disulfide bond formation.

[0741] Yet another class of sulfhydryl reactive groups forms thioether bonds with sulfhydryl groups. Such groups include, inter alia, maleimido, substituted maleimido, haloalkyl, epoxy, imino, and aziridino, as well as olefins (including conjugated olefins) such as ethenesulfonyl, eteneimino, acrylate, methacrylate, and α,β-unsaturated aldehydes and ketones.

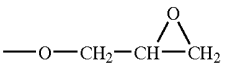
[0742] When X is —OH, the electrophilic functional groups on the remaining component(s) must react with hydroxyl groups. The hydroxyl group may be activated as described above with respect to carboxylic acid groups, or it may react directly in the presence of base with a sufficiently reactive electrophilic group such as an epoxide group, an aziridine group, an acyl halide, an anhydride, and so forth.

[0743] When X is an organometallic nucleophilic group such as a Grignard functionality or an alkyllithium group, suitable electrophilic functional groups for reaction therewith are those containing carbonyl groups, including, by way of example, ketones and aldehydes.

[0744] It will also be appreciated that certain functional groups can react as nucleophilic or as electrophilic groups, depending on the selected reaction partner and/or the reaction conditions. For example, a carboxylic acid group can act as a nucleophilic group in the presence of a fairly strong base, but generally acts as an electrophilic group allowing nucleophilic attack at the carbonyl carbon and concomitant replacement of the hydroxyl group with the incoming nucleophilic group.

[0745] These, as well as other embodiments are illustrated below, where the covalent linkages in the matrix that result upon covalent binding of specific nucleophilic reactive groups to specific electrophilic reactive groups on the self-reactive compound include, solely by way of example, the following Table:

TABLE

Representative Nucleophilic Group (X, Z_{NU})	Representative Electrophilic Group (Y, Z_{EL})	Resulting Linkage
—NH_2	—O—(CO)—O—$N(COCH_2)_2$ succinimidyl carbonate terminus	—NH—(CO)—O—
—SH	—O—(CO)—O—$N(COCH_2)_2$	—S—(CO)—O—
—OH	—O—(CO)—O—$N(COCH_2)_2$	—O—(CO)—
—NH_2	—O(CO)—CH=CH_2 acrylate terminus	—NH—CH_2CH_2—(CO)—O—
—SH	—O—(CO)—CH=CH_2	—S—CH_2CH_2—(CO)—O—
—OH	—O—(CO)—CH=CH_2	—O—CH_2CH_2—(CO)—O—
—NH_2	—O(CO)—$(CH_2)_3$—CO_2—$N(COCH_2)_2$ succinimidyl glutarate terminus	—NH—(CO)—$(CH_2)_3$—(CO)—O—
—SH	—O(CO)—$(CH_2)_3$—CO_2—$N(COCH_2)_2$	—S—(CO)—$(CH_2)_3$—(CO)—O—
—OH	—O(CO)—$(CH_2)_3$—CO_2—$N(COCH_2)_2$	—O—(CO)—$(CH_2)_3$—(CO)—O—
—NH_2	—O—CH_2—CO_2—$N(COCH_2)_2$ succinimidyl acetate terminus	—NH—(CO)—CH_2—O—
—SH	—O—CH_2—CO_2—$N(COCH_2)_2$	—S—(CO)—CH_2—O—
—OH	—O—CH_2—CO_2—$N(COCH_2)_2$	—O—(CO)—CH_2—O—
—NH_2	—O—NH(CO)—$(CH_2)_2$—CO_2—$N(COCH_2)_2$ succinimidyl succinamide terminus	—NH—(CO)—$(CH_2)_2$—(CO)—NH—O
—SH	—O—NH(CO)—$(CH_2)_2$—CO_2—$N(COCH_2)_2$	—S—(CO)—$(CH_2)_2$—(CO)—NH—O—
—OH	—O—NH(CO)—$(CH_2)_2$—CO_2—$N(COCH_2)_2$	—O—(CO)—$(CH_2)_2$—(CO)—NH—O—
—NH_2	—O—$(CH_2)_2$—CHO propionaldehyde terminus	—NH—(CO)—$(CH_2)_2$—O—
—NH_2	 glycidyl ether terminus	—NH—CH_2—CH(OH)—CH_2—O— and —N[CH_2—CH(OH)—CH_2—O—]$_2$
—NH_2	—O—$(CH_2)_2$—N=C=O (isocyanate terminus)	—NH—(CO)—NH—CH_2—O—
—NH_2	—SO_2—CH=CH_2 vinyl sulfone terminus	—NH—CH_2CH_2—SO_2—
—SH	—SO_2—CH=CH_2	—S—CH_2CH_2—SO_2—

[0746] For self-reactive compounds containing electrophilic and nucleophilic reactive groups, the initial environment typically can be dry and sterile. Since electrophilic groups react with water, storage in sterile, dry form will prevent hydrolysis. The dry synthetic polymer may be compression molded into a thin sheet or membrane, which can then be sterilized using gamma or e-beam irradiation. The resulting dry membrane or sheet can be cut to the desired size or chopped into smaller size particulates. The modification of a dry initial environment will typically comprise the addition of an aqueous medium.

[0747] In one embodiment, the initial environment can be an aqueous medium such as in a low pH buffer, i.e., having a pH less than about 6.0, in which both electrophilic and nucleophilic groups are non-reactive. Suitable liquid media for storage of such compounds include aqueous buffer solutions such as monobasic sodium phosphate/dibasic sodium phosphate, sodium carbonate/sodium bicarbonate, glutamate or acetate, at a concentration of 0.5 to 300 mM. Modification of an initial low pH aqueous environment will typically comprise increasing the pH to at least pH 7.0, more preferably increasing the pH to at least pH 9.5.

[0748] In another embodiment the modification of a dry initial environment comprises dissolving the self-reactive compound in a first buffer solution having a pH within the range of about 1.0 to 5.5 to form a homogeneous solution, and (ii) adding a second buffer solution having a pH within the range of about 6.0 to 11.0 to the homogeneous solution. The buffer solutions are aqueous and can be any pharmaceutically acceptable basic or acid composition. The term "buffer" is used in a general sense to refer to an acidic or basic aqueous solution, where the solution may or may not be functioning to provide a buffering effect (i.e., resistance to change in pH upon addition of acid or base) in the compositions of the present invention. For example, the self-reactive compound can be in the form of a homogeneous dry powder. This powder is then combined with a buffer solution having a pH within the range of about 1.0 to 5.5 to form a homogeneous acidic aqueous solution, and this solution is then combined with a buffer solution having a pH within the range of about 6.0 to 11.0 to form a reactive solution. For example, 0.375 grams of the dry powder can be combined with 0.75 grams of the acid buffer to provide, after mixing, a homogeneous solution, where this solution is combined with 1.1 grams of the basic buffer to provide a reactive mixture that substantially immediately forms a three-dimensional matrix.

[0749] Acidic buffer solutions having a pH within the range of about 1.0 to 5.5, include by way of illustration and not limitation, solutions of: citric acid, hydrochloric acid, phosphoric acid, sulfuric acid, AMPSO (3-[(1,1-dimethyl-2-hydroxyethyl)amino]2-hydroxy-propane-sulfonic acid),

acetic acid, lactic acid, and combinations thereof. In a preferred embodiment, the acidic buffer solution is a solution of citric acid, hydrochloric acid, phosphoric acid, sulfuric acid, and combinations thereof. Regardless of the precise acidifying agent, the acidic buffer preferably has a pH such that it retards the reactivity of the nucleophilic groups on the core. For example, a pH of 2.1 is generally sufficient to retard the nucleophilicity of thiol groups. A lower pH is typically preferred when the core contains amine groups as the nucleophilic groups. In general, the acidic buffer is an acidic solution that, when contacted with nucleophilic groups, renders those nucleophilic groups relatively non-nucleophilic.

[0750] An exemplary acidic buffer is a solution of hydrochloric acid, having a concentration of about 6.3 mM and a pH in the range of 2.1 to 2.3. This buffer may be prepared by combining concentrated hydrochloric acid with water, i.e., by diluting concentrated hydrochloric acid with water. Similarly, this buffer A may also be conveniently prepared by diluting 1.23 grams of concentrated hydrochloric acid to a volume of 2 liters, or diluting 1.84 grams of concentrated hydrochloric acid to a volume to 3 liters, or diluting 2.45 grams of concentrated hydrochloric acid to a volume of 4 liters, or diluting 3.07 grams concentrated hydrochloric acid to a volume of 5 liters, or diluting 3.68 grams of concentrated hydrochloric acid to a volume to 6 liters. For safety reasons, the concentrated acid is preferably added to water.

[0751] Basic buffer solutions having a pH within the range of about 6.0 to 11.0, include by way of illustration and not limitation, solutions of: glutamate, acetate, carbonate and carbonate salts (e.g., sodium carbonate, sodium carbonate monohydrate and sodium bicarbonate), borate, phosphate and phosphate salts (e.g., monobasic sodium phosphate monohydrate and dibasic sodium phosphate), and combinations thereof. In a preferred embodiment, the basic buffer solution is a solution of carbonate salts, phosphate salts, and combinations thereof.

[0752] In general, the basic buffer is an aqueous solution that neutralizes the effect of the acidic buffer, when it is added to the homogeneous solution of the compound and first buffer, so that the nucleophilic groups on the core regain their nucleophilic character (that has been masked by the action of the acidic buffer), thus allowing the nucleophilic groups to inter-react with the electrophilic groups on the core.

[0753] An exemplary basic buffer is an aqueous solution of carbonate and phosphate salts. This buffer may be prepared by combining a base solution with a salt solution. The salt solution may be prepared by combining 34.7 g of monobasic sodium phosphate monohydrate, 49.3 g of sodium carbonate monohydrate, and sufficient water to provide a solution volume of 2 liter. Similarly, a 6 liter solution may be prepared by combining 104.0 g of monobasic sodium phosphate monohydrate, 147.94 g of sodium carbonate monohydrate, and sufficient water to provide 6 liter of the salt solution. The basic buffer may be prepared by combining 7.2 g of sodium hydroxide with 180.0 g of water. The basic buffer is typically prepared by adding the base solution as needed to the salt solution, ultimately to provide a mixture having the desired pH, e.g., a pH of 9.65 to 9.75.

[0754] In general, the basic species present in the basic buffer should be sufficiently basic to neutralize the acidity provided by the acidic buffer, but should not be so nucleophilic itself that it will react substantially with the electrophilic groups on the core. For this reason, relatively "soft" bases such as carbonate and phosphate are preferred in this embodiment of the invention.

[0755] To illustrate the preparation of a three-dimensional matrix of the present invention, one may combine an admixture of the self-reactive compound with a first, acidic, buffer (e.g., an acid solution, e.g., a dilute hydrochloric acid solution) to form a homogeneous solution. This homogeneous solution is mixed with a second, basic, buffer (e.g., a basic solution, e.g., an aqueous solution containing phosphate and carbonate salts) whereupon the reactive groups on the core of the self-reactive compound substantially immediately inter-react with one another to form a three-dimensional matrix.

[0756] 2) Redox Reactive Groups

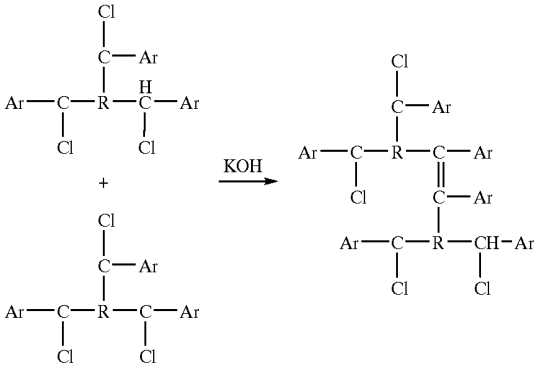
[0757] In one embodiment of the invention, the reactive groups are vinyl groups such as styrene derivatives, which undergo a radical polymerization upon initiation with a redox initiator. The term "redox" refers to a reactive group that is susceptible to oxidation-reduction activation. The term "vinyl" refers to a reactive group that is activated by a redox initiator, and forms a radical upon reaction. X, Y and Z can be the same or different vinyl groups, for example, methacrylic groups.

[0758] For self-reactive compounds containing vinyl reactive groups, the initial environment typically will be an aqueous environment. The modification of the initial environment involves the addition of a redox initiator.

[0759] 3) Oxidative Coupling Reactive Groups

[0760] In one embodiment of the invention, the reactive groups undergo an oxidative coupling reaction. For example, X, Y and Z can be a halo group such as chloro, with an adjacent electron-withdrawing group on the halogen-bearing carbon (e.g., on the "L" linking group). Exemplary electron-withdrawing groups include nitro, aryl, and so forth.

[0761] For such reactive groups, the modification in the initial environment comprises a change in pH. For example, in the presence of a base such as KOH, the self-reactive compounds then undergo a de-hydro, chloro coupling reaction, forming a double bond between the carbon atoms, as illustrated below:

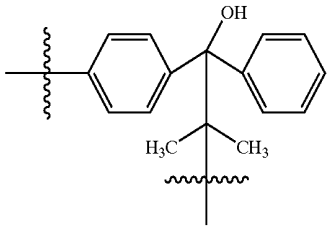


[0762] For self-reactive compounds containing oxidative coupling reactive groups, the initial environment typically can be can be dry and sterile, or a non-basic medium. The modification of the initial environment will typically comprise the addition of a base.

[0763] 4) Photoinitiated Reactive Groups

[0764] In one embodiment of the invention, the reactive groups are photoinitiated groups. For such reactive groups, the modification in the initial environment comprises exposure to ultraviolet radiation.

[0765] In one embodiment of the invention, X can be an azide ($—N_3$) group and Y can be an alkyl group such as $—CH(CH_3)_2$ or vice versa. Exposure to ultraviolet radiation will then form a bond between the groups to provide for the following linkage: $—NH—C(CH_3)_2—CH_2—$. In another embodiment of the invention, X can be a benzophenone ($—(C_6H_4)—C(O)—(C_6H_5)$) group and Y can be an alkyl group such as $—CH(CH_3)_2$ or vice versa. Exposure to ultraviolet radiation will then form a bond between the groups to provide for the following linkage:



[0766] For self-reactive compounds containing photoinitiated reactive groups, the initial environment typically will be in an ultraviolet radiation-shielded environment. This can be for example, storage within a container that is impermeable to ultraviolet radiation.

[0767] The modification of the initial environment will typically comprise exposure to ultraviolet radiation.

[0768] 5) Temperature-Sensitive Reactive Groups

[0769] In one embodiment of the invention, the reactive groups are temperature-sensitive groups, which undergo a thermochemical reaction. For such reactive groups, the modification in the initial environment thus comprises a change in temperature. The term "temperature-sensitive" refers to a reactive group that is chemically inert at one temperature or temperature range and reactive at a different temperature or temperature range.

[0770] In one embodiment of the invention, X, Y, and Z are the same or different vinyl groups.

[0771] For self-reactive compounds containing reactive groups that are temperature-sensitive, the initial environment typically will be within the range of about 10 to 30° C.

[0772] The modification of the initial environment will typically comprise changing the temperature to within the range of about 20 to 40° C.

[0773] F. Linking Groups

[0774] The reactive groups may be directly attached to the core, or they may be indirectly attached through a linking group, with longer linking groups also termed "chain extenders." In the formula (I) shown above, the optional linker groups are represented by L^1, L^2, and L^3, wherein the linking groups are present when p, q and r are equal to 1.

[0775] Suitable linking groups are well known in the art. See, for example, WO 97/22371 to Rhee et al. Linking groups are useful to avoid steric hindrance problems that can sometimes associated with the formation of direct linkages between molecules. Linking groups may additionally be used to link several self-reactive compounds together to make larger molecules. In one embodiment, a linking group can be used to alter the degradative properties of the compositions after administration and resultant gel formation. For example, linking groups can be used to promote hydrolysis, to discourage hydrolysis, or to provide a site for enzymatic degradation.

[0776] Examples of linking groups that provide hydrolyzable sites, include, inter alia: ester linkages; anhydride linkages, such as those obtained by incorporation of glutarate and succinate; ortho ester linkages; ortho carbonate linkages such as trimethylene carbonate; amide linkages; phosphoester linkages; α-hydroxy acid linkages, such as those obtained by incorporation of lactic acid and glycolic acid; lactone-based linkages, such as those obtained by incorporation of caprolactone, valerolactone, γ-butyrolactone and p-dioxanone; and amide linkages such as in a dimeric, oligomeric, or poly(amino acid) segment. Examples of non-degradable linking groups include succinimide, propionic acid and carboxymethylate linkages. See, for example, WO 99/07417 to Coury et al. Examples of enzymatically degradable linkages include Leu-Gly-Pro-Ala, which is degraded by collagenase; and Gly-Pro-Lys, which is degraded by plasmin.

[0777] Linking groups can also be included to enhance or suppress the reactivity of the various reactive groups. For example, electron-withdrawing groups within one or two carbons of a sulfhydryl group would be expected to diminish its effectiveness in coupling, due to a lowering of nucleophilicity. Carbon-carbon double bonds and carbonyl groups will also have such an effect. Conversely, electron-withdrawing groups adjacent to a carbonyl group (e.g., the reactive carbonyl of glutaryl-N-hydroxysuccinimidyl) would increase the reactivity of the carbonyl carbon with respect to an incoming nucleophilic group. By contrast, sterically bulky groups in the vicinity of a reactive group can be used to diminish reactivity and thus reduce the coupling rate as a result of steric hindrance.

[0778] By way of example, particular linking groups and corresponding formulas are indicated in the following Table:

TABLE

Linking group	Component structure
$—O—(CH_2)_x—$	$—O—(CH_2)_x—X$ $—O—(CH_2)_x—Y$ $—O—(CH_2)_x—Z$
$—S—(CH_2)_x—$	$—S—(CH_2)_x—X$ $—S—(CH_2)_x—Y$ $—S—(CH_2)_x—Z$
$—NH—(CH_2)_x—$	$—NH—(CH_2)_x—X$ $—NH—(CH_2)_x—Y$ $—NH—(CH_2)_x—Z$

TABLE-continued

Linking group	Component structure
—O—(CO)—NH—$(CH_2)_x$—	—O—(CO)—NH—$(CH_2)_x$—X —O—(CO)—NH—$(CH_2)_x$—Y —O—(CO)—NH—$(CH_2)_x$—Z
—NH—(CO)—O—$(CH_2)_x$—	—NH—(CO)—O—$(CH_2)_x$—X —NH—(CO)—O—$(CH_2)_x$—Y —NH—(CO)—O—$(CH_2)_x$—Z
—O—(CO)—$(CH_2)_x$—	—O—(CO)—$(CH_2)_x$—X —O—(CO)—$(CH_2)_x$—Y —O—(CO)—$(CH_2)_x$—Z
—(CO)—O—$(CH_2)_x$—	—(CO)—O—$(CH_2)_n$—X —(CO)—O—$(CH_2)_n$—Y —(CO)—O—$(CH_2)_n$—Z
—O—(CO)—O—$(CH_2)_x$—	—O—(CO)—O—$(CH_2)_x$—X —O—(CO)—O—$(CH_2)_x$—Y —O—(CO)—O—$(CH_2)_x$—Z
—O—(CO)—CHR^2—	—O—(CO)—CHR^2—X —O—(CO)—CHR^2—Y —O—(CO)—CHR^2—Z
—O—R^3—(CO)—NH—	—O—R^3—(CO)—NH—X —O—R^3—(CO)—NH—Y —O—R^3—(CO)—NH—Z

[0779] In the above Table, x is generally in the range of 1 to about 10; R^2 is generally hydrocarbyl, typically alkyl or aryl, preferably alkyl, and most preferably lower alkyl; and R^3 is hydrocarbylene, heteroatom-containing hydrocarbylene, substituted hydrocarbylene, or substituted heteroatom-containing hydrocarbylene) typically alkylene or arylene (again, optionally substituted and/or containing a heteroatom), preferably lower alkylene (e.g., methylene, ethylene, n-propylene, n-butylene, etc.), phenylene, or amidoalkylene (e.g., —(CO)—NH—CH_2).

[0780] Other general principles that should be considered with respect to linking groups are as follows. If a higher molecular weight self-reactive compound is to be used, it will preferably have biodegradable linkages as described above, so that fragments larger than 20,000 mol. wt. are not generated during resorption in the body. In addition, to promote water miscibility and/or solubility, it may be desired to add sufficient electric charge or hydrophilicity. Hydrophilic groups can be easily introduced using known chemical synthesis, so long as they do not give rise to unwanted swelling or an undesirable decrease in compressive strength. In particular, polyalkoxy segments may weaken gel strength.

[0781] G. The Core

[0782] The "core" of each self-reactive compound is comprised of the molecular structure to which the reactive groups are bound. The molecular core can a polymer, which includes synthetic polymers and naturally occurring polymers. In one embodiment, the core is a polymer containing repeating monomer units. The polymers can be hydrophilic, hydrophobic, or amphiphilic. The molecular core can also be a low molecular weight components such as a C_{2-14} hydrocarbyl or a heteroatom-containing C_{2-14} hydrocarbyl. The heteroatom-containing C_{2-14} hydrocarbyl can have 1 or 2 heteroatoms selected from N, O and S. In a preferred embodiment, the self-reactive compound comprises a molecular core of a synthetic hydrophilic polymer.

[0783] 1) Hydrophilic Polymers

[0784] As mentioned above, the term "hydrophilic polymer" as used herein refers to a polymer having an average molecular weight and composition that naturally renders, or is selected to render the polymer as a whole "hydrophilic." Preferred polymers are highly pure or are purified to a highly pure state such that the polymer is or is treated to become pharmaceutically pure. Most hydrophilic polymers can be rendered water soluble by incorporating a sufficient number of oxygen (or less frequently nitrogen) atoms available for forming hydrogen bonds in aqueous solutions.

[0785] Synthetic hydrophilic polymers may be homopolymers, block copolymers including di-block and tri-block copolymers, random copolymers, or graft copolymers. In addition, the polymer may be linear or branched, and if branched, may be minimally to highly branched, dendrimeric, hyperbranched, or a star polymer. The polymer may include biodegradable segments and blocks, either distributed throughout the polymer's molecular structure or present as a single block, as in a block copolymer. Biodegradable segments preferably degrade so as to break covalent bonds. Typically, biodegradable segments are segments that are hydrolyzed in the presence of water and/or enzymatically cleaved in situ. Biodegradable segments may be composed of small molecular segments such as ester linkages, anhydride linkages, ortho ester linkages, ortho carbonate linkages, amide linkages, phosphonate linkages, etc. Larger biodegradable "blocks" will generally be composed of oligomeric or polymeric segments incorporated within the hydrophilic polymer. Illustrative oligomeric and polymeric segments that are biodegradable include, by way of example, poly(amino acid) segments, poly(orthoester) segments, poly(orthocarbonate) segments, and the like. Other biodegradable segments that may form part of the hydrophilic polymer core include polyesters such as polylactide, polyethers such as polyalkylene oxide, polyamides such as a protein, and polyurethanes. For example, the core of the self-reactive compound can be a diblock copolymer of tetrafunctionally activated polyethylene glycol and polylactide.

[0786] Synthetic hydrophilic polymers that are useful herein include, but are not limited to: polyalkylene oxides, particularly polyethylene glycol (PEG) and poly(ethylene oxide)-poly(propylene oxide) copolymers, including block and random copolymers; polyols such as glycerol, polyglycerol (PG) and particularly highly branched polyglycerol, propylene glycol; poly(oxyalkylene)-substituted diols, and poly(oxyalkylene)-substituted polyols such as mono-, di- and tri-polyoxyethylated glycerol, mono- and di-polyoxyethylated propylene glycol, and mono- and di-polyoxyethylated trimethylene glycol; polyoxyethylated sorbitol, polyoxyethylated glucose; poly(acrylic acids) and analogs and copolymers thereof, such as polyacrylic acid per se, polymethacrylic acid, poly(hydroxyethylmethacrylate), poly(hydroxyethylacrylate), poly(methylalkylsulfoxide methacrylates), poly(methylalkylsulfoxide acrylates) and copolymers of any of the foregoing, and/or with additional acrylate species such as aminoethyl acrylate and mono-2-(acryloxy)-ethyl succinate; polymaleic acid; poly(acrylamides) such as polyacrylamide per se, poly(methacrylamide), poly(dimethylacrylamide), poly(N-isopropyl-acrylamide), and copolymers thereof; poly(olefinic alcohols) such as poly(vinyl alcohols) and copolymers thereof; poly(N-vinyl lactams) such as poly(vinyl pyrrolidones), poly(N-vinyl caprolactams), and copolymers thereof; polyoxazolines, including poly(methyloxazoline) and poly(ethyloxazoline); and polyvinylamines; as well as copolymers of any of the foregoing.

It must be emphasized that the aforementioned list of polymers is not exhaustive, and a variety of other synthetic hydrophilic polymers may be used, as will be appreciated by those skilled in the art.

[0787] Those of ordinary skill in the art will appreciate that synthetic polymers such as polyethylene glycol cannot be prepared practically to have exact molecular weights, and that the term "molecular weight" as used herein refers to the weight average molecular weight of a number of molecules in any given sample, as commonly used in the art. Thus, a sample of PEG 2,000 might contain a statistical mixture of polymer molecules ranging in weight from, for example, 1,500 to 2,500 daltons with one molecule differing slightly from the next over a range. Specification of a range of molecular weights indicates that the average molecular weight may be any value between the limits specified, and may include molecules outside those limits. Thus, a molecular weight range of about 800 to about 20,000 indicates an average molecular weight of at least about 800, ranging up to about 20 kDa.

[0788] Other suitable synthetic hydrophilic polymers include chemically synthesized polypeptides, particularly polynucleophilic polypeptides that have been synthesized to incorporate amino acids containing primary amino groups (such as lysine) and/or amino acids containing thiol groups (such as cysteine). Poly(lysine), a synthetically produced polymer of the amino acid lysine (145 MW), is particularly preferred. Poly(lysine)s have been prepared having anywhere from 6 to about 4,000 primary amino groups, corresponding to molecular weights of about 870 to about 580, 000. Poly(lysine)s for use in the present invention preferably have a molecular weight within the range of about 1,000 to about 300,000, more preferably within the range of about 5,000 to about 100,000, and most preferably, within the range of about 8,000 to about 15,000. Poly(lysine)s of varying molecular weights are commercially available from Peninsula Laboratories, Inc. (Belmont, Calif.).

[0789] Although a variety of different synthetic hydrophilic polymers can be used in the present compounds, preferred synthetic hydrophilic polymers are PEG and PG, particularly highly branched PG. Various forms of PEG are extensively used in the modification of biologically active molecules because PEG lacks toxicity, antigenicity, and immunogenicity (i.e., is biocompatible), can be formulated so as to have a wide range of solubilities, and does not typically interfere with the enzymatic activities and/or conformations of peptides. A particularly preferred synthetic hydrophilic polymer for certain applications is a PEG having a molecular weight within the range of about 100 to about 100,000, although for highly branched PEG, far higher molecular weight polymers can be employed, up to 1,000, 000 or more, providing that biodegradable sites are incorporated ensuring that all degradation products will have a molecular weight of less than about 30,000. For most PEGs, however, the preferred molecular weight is about 1,000 to about 20,000, more preferably within the range of about 7,500 to about 20,000. Most preferably, the polyethylene glycol has a molecular weight of approximately 10,000.

[0790] Naturally occurring hydrophilic polymers include, but are not limited to: proteins such as collagen, fibronectin, albumins, globulins, fibrinogen, fibrin and thrombin, with collagen particularly preferred; carboxylated polysaccharides such as polymannuronic acid and polygalacturonic acid; aminated polysaccharides, particularly the glycosaminoglycans, e.g., hyaluronic acid, chitin, chondroitin sulfate A, B, or C, keratin sulfate, keratosulfate and heparin; and activated polysaccharides such as dextran and starch derivatives. Collagen and glycosaminoglycans are preferred naturally occurring hydrophilic polymers for use herein.

[0791] Unless otherwise specified, the term "collagen" as used herein refers to all forms of collagen, including those, which have been processed or otherwise modified. Thus, collagen from any source may be used in the compounds of the invention; for example, collagen may be extracted and purified from human or other mammalian source, such as bovine or porcine corium and human placenta, or may be recombinantly or otherwise produced. The preparation of purified, substantially non-antigenic collagen in solution from bovine skin is well known in the art. For example, U.S. Pat. No. 5,428,022 to Palefsky et al. discloses methods of extracting and purifying collagen from the human placenta, and U.S. Pat. No. 5,667,839 to Berg discloses methods of producing recombinant human collagen in the milk of transgenic animals, including transgenic cows. Non-transgenic, recombinant collagen expression in yeast and other cell lines) is described in U.S. Pat. No. 6,413,742 to Olsen et al., 6,428,978 to Olsen et al., and 6,653,450 to Berg et al.

[0792] Collagen of any type, including, but not limited to, types I, II, III, IV, or any combination thereof, may be used in the compounds of the invention, although type I is generally preferred. Either atelopeptide or telopeptide-containing collagen may be used; however, when collagen from a natural source, such as bovine collagen, is used, atelopeptide collagen is generally preferred, because of its reduced immunogenicity compared to telopeptide-containing collagen.

[0793] Collagen that has not been previously crosslinked by methods such as heat, irradiation, or chemical crosslinking agents is preferred for use in the invention, although previously crosslinked collagen may be used.

[0794] Collagens for use in the present invention are generally, although not necessarily, in aqueous suspension at a concentration between about 20 mg/ml to about 120 mg/ml, preferably between about 30 mg/ml to about 90 mg/ml. Although intact collagen is preferred, denatured collagen, commonly known as gelatin, can also be used. Gelatin may have the added benefit of being degradable faster than collagen.

[0795] Nonfibrillar collagen is generally preferred for use in compounds of the invention, although fibrillar collagens may also be used. The term "nonfibrillar collagen" refers to any modified or unmodified collagen material that is in substantially nonfibrillar form, i.e., molecular collagen that is not tightly associated with other collagen molecules so as to form fibers. Typically, a solution of nonfibrillar collagen is more transparent than is a solution of fibrillar collagen. Collagen types that are nonfibrillar (or microfibrillar) in native form include types IV, VI, and VII.

[0796] Chemically modified collagens that are in nonfibrillar form at neutral pH include succinylated collagen and methylated collagen, both of which can be prepared according to the methods described in U.S. Pat. No. 4,164, 559 to Miyata et al. Methylated collagen, which contains

reactive amine groups, is a preferred nucleophile-containing component in the compositions of the present invention. In another aspect, methylated collagen is a component that is present in addition to first and second components in the matrix-forming reaction of the present invention. Methylated collagen is described in, for example, in U.S. Pat. No. 5,614,587 to Rhee et al.

[0797] Collagens for use in the compositions of the present invention may start out in fibrillar form, then can be rendered nonfibrillar by the addition of one or more fiber disassembly agent. The fiber disassembly agent must be present in an amount sufficient to render the collagen substantially nonfibrillar at pH 7, as described above. Fiber disassembly agents for use in the present invention include, without limitation, various biocompatible alcohols, amino acids, inorganic salts, and carbohydrates, with biocompatible alcohols being particularly preferred. Preferred biocompatible alcohols include glycerol and propylene glycol. Non-biocompatible alcohols, such as ethanol, methanol, and isopropanol, are not preferred for use in the present invention, due to their potentially deleterious effects on the body of the patient receiving them. Preferred amino acids include arginine. Preferred inorganic salts include sodium chloride and potassium chloride. Although carbohydrates, such as various sugars including sucrose, may be used in the practice of the present invention, they are not as preferred as other types of fiber disassembly agents because they can have cytotoxic effects in vivo.

[0798] Fibrillar collagen is less preferred for use in the compounds of the invention. However, as disclosed in U.S. Pat. No. 5,614,587 to Rhee et al., fibrillar collagen, or mixtures of nonfibrillar and fibrillar collagen, may be preferred for use in compounds intended for long-term persistence in vivo.

[0799] 2) Hydrophobic Polymers

[0800] The core of the self-reactive compound may also comprise a hydrophobic polymer, including low molecular weight polyfunctional species, although for most uses hydrophilic polymers are preferred. Generally, "hydrophobic polymers" herein contain a relatively small proportion of oxygen and/or nitrogen atoms. Preferred hydrophobic polymers for use in the invention generally have a carbon chain that is no longer than about 14 carbons. Polymers having carbon chains substantially longer than 14 carbons generally have very poor solubility in aqueous solutions and, as such, have very long reaction times when mixed with aqueous solutions of synthetic polymers containing, for example, multiple nucleophilic groups. Thus, use of short-chain oligomers can avoid solubility-related problems during reaction. Polylactic acid and polyglycolic acid are examples of two particularly suitable hydrophobic polymers.

[0801] 3) Amphiphilic Polymers

[0802] Generally, amphiphilic polymers have a hydrophilic portion and a hydrophobic (or lipophilic) portion. The hydrophilic portion can be at one end of the core and the hydrophobic portion at the opposite end, or the hydrophilic and hydrophobic portions may be distributed randomly (random copolymer) or in the form of sequences or grafts (block copolymer) to form the amphiphilic polymer core of the self-reactive compound. The hydrophilic and hydrophobic portions may include any of the aforementioned hydrophilic and hydrophobic polymers.

[0803] Alternately, the amphiphilic polymer core can be a hydrophilic polymer that has been modified with hydrophobic moieties (e.g., alkylated PEG or a hydrophilic polymer modified with one or more fatty chains), or a hydrophobic polymer that has been modified with hydrophilic moieties (e.g., "PEGylated" phospholipids such as polyethylene glycolated phospholipids).

[0804] 4) Low Molecular Weight Components

[0805] As indicated above, the molecular core of the self-reactive compound can also be a low molecular weight compound, defined herein as being a C_{2-14} hydrocarbyl or a heteroatom-containing C_{2-14} hydrocarbyl, which contains 1 to 2 heteroatoms selected from N, O, S and combinations thereof. Such a molecular core can be substituted with any of the reactive groups described herein.

[0806] Alkanes are suitable C_{2-14} hydrocarbyl molecular cores. Exemplary alkanes, for substituted with a nucleophilic primary amino group and a Y electrophilic group, include, ethyleneamine (H_2N—CH_2CH_2—Y), tetramethyleneamine (H_2N—(CH_4)—Y), pentamethyleneamine (H_2N—(CH_5)—Y), and hexamethyleneamine (H_2N—(CH_6)—Y).

[0807] Low molecular weight diols and polyols are also suitable C_{2-14} hydrocarbyls and include trimethylolpropane, di(trimethylol propane), pentaerythritol, and diglycerol. Polyacids are also suitable C_{2-14} hydrocarbyls, and include trimethylolpropane-based tricarboxylic acid, di(trimethylol propane)-based tetracarboxylic acid, heptanedioic acid, octanedioic acid (suberic acid), and hexadecanedioic acid (thapsic acid).

[0808] Low molecular weight di- and poly-electrophiles are suitable heteroatom-containing C_{2-14} hydrocarbyl molecular cores. These include, for example, disuccinimidyl suberate (DSS), bis(sulfosuccinimidyl) suberate (BS_3), dithiobis(succinimidylpropionate) (DSP), bis(2-succinimidooxycarbonyloxy) ethyl sulfone (BSOCOES), and 3,3'-dithiobis(sulfosuccinimidylpropionate (DTSPP), and their analogs and derivatives.

[0809] In one embodiment of the invention, the self-reactive compound of the invention comprises a low-molecular weight material core, with a plurality of acrylate moieties and a plurality of thiol groups.

[0810] H. Preparation

[0811] The self-reactive compounds are readily synthesized to contain a hydrophilic, hydrophobic or amphiphilic polymer core or a low molecular weight core, functionalized with the desired functional groups, i.e., nucleophilic and electrophilic groups, which enable crosslinking. For example, preparation of a self-reactive compound having a polyethylene glycol (PEG) core is discussed below. However, it is to be understood that the following discussion is for purposes of illustration and analogous techniques may be employed with other polymers.

[0812] With respect to PEG, first of all, various functionalized PEGs have been used effectively in fields such as protein modification (see Abuchowski et al., Enzymes as Drugs, John Wiley & Sons: New York, N.Y. (1981) pp. 367-383; and Dreborg et al. (1990) *Crit. Rev. Therap. Drug Carrier Syst.* 6:315), peptide chemistry (see Mutter et al., The Peptides, Academic: New York, N.Y. 2:285-332; and

Zalipsky et al. (1987) *Int. J. Peptide Protein Res.* 30:740), and the synthesis of polymeric drugs (see Zalipsky et al. (1983) *Eur. Polym. J.* 19:1177; and Ouchi et al. (1987) *J. Macromol. Sci. Chem.* A24:1011).

[0813] Functionalized forms of PEG, including multi-functionalized PEG, are commercially available, and are also easily prepared using known methods. For example, see Chapter 22 of Poly(ethylene Glycol) Chemistry: Biotechnical and Biomedical Applications, J. Milton Harris, ed., Plenum Press, NY (1992).

[0814] Multi-functionalized forms of PEG are of particular interest and include, PEG succinimidyl glutarate, PEG succinimidyl propionate, succinimidyl butylate, PEG succinimidyl acetate, PEG succinimidyl succinamide, PEG succinimidyl carbonate, PEG propionaldehyde, PEG glycidyl ether, PEG-isocyanate, and PEG-vinylsulfone. Many such forms of PEG are described in U.S. Pat. Nos. 5,328,955 and 6,534,591, both to Rhee et al. Similarly, various forms of multi-amino PEG are commercially available from sources such as PEG Shop, a division of SunBio of South Korea (www.sunbio.com), Nippon Oil and Fats (Yebisu Garden Place Tower, 20-3 Ebisu 4-chome, Shibuya-ku, Tokyo), Nektar Therapeutics (San Carlos, Calif., formerly Shearwater Polymers, Huntsville, Ala.) and from Huntsman's Performance Chemicals Group (Houston, Tex.) under the name Jeffamine® polyoxyalkyleneamines. Multi-amino PEGs useful in the present invention include the Jeffamine diamines ("D" series) and triamines ("T" series), which contain two and three primary amino groups per molecule. Analogous poly(sulfhydryl) PEGs are also available from Nektar Therapeutics, e.g., in the form of pentaerythritol poly(ethylene glycol) ether tetra-sulfhydryl (molecular weight 10,000). These multi-functionalized forms of PEG can then be modified to include the other desired reactive groups.

[0815] Reaction with succinimidyl groups to convert terminal hydroxyl groups to reactive esters is one technique for preparing a core with electrophilic groups. This core can then be modified include nucleophilic groups such as primary amines, thiols, and hydroxyl groups. Other agents to convert hydroxyl groups include carbonyldiimidazole and sulfonyl chloride. However, as discussed herein, a wide variety of electrophilic groups may be advantageously employed for reaction with corresponding nucleophilic groups. Examples of such electrophilic groups include acid chloride groups; anhydrides, ketones, aldehydes, isocyanate, isothiocyanate, epoxides, and olefins, including conjugated olefins such as ethenesulfonyl ($—SO_2CH═CH_2$) and analogous functional groups.

[0816] Other In Situ Crosslinking Materials

[0817] Numerous other types of in situ forming materials have been described which may be used in combination with an anti-scarring agent in accordance with the invention. The in situ forming material may be a biocompatible crosslinked polymer that is formed from water soluble precursors having electrophilic and nucleophilic groups capable of reacting and crosslinking in situ (see, e.g., U.S. Pat. No. 6,566,406). The in situ forming material may be hydrogel that may be formed through a combination of physical and chemical crosslinking processes, where physical crosslinking is mediated by one or more natural or synthetic components that stabilize the hydrogel-forming precursor solution at a deposition site for a period of time sufficient for more resilient chemical crosslinks to form (see, e.g., U.S. Pat. No. 6,818,018). The in situ forming material may be formed upon exposure to an aqueous fluid from a physiological environment from dry hydrogel precursors (see, e.g., U.S. Pat. No. 6,703,047). The in situ forming material may be a hydrogel matrix that provides controlled release of relatively low molecular weight therapeutic species by first dispersing or dissolving the therapeutic species within relatively hydrophobic rate modifying agents to form a mixture; the mixture is formed into microparticles that are dispersed within bioabsorbable hydrogels, so as to release the water soluble therapeutic agents in a controlled fashion (see, e.g., U.S. Pat. No. 6,632,457). The in situ forming material may be a multi-component hydrogel system (see, e.g., U.S. Pat. No. 6,379,373). The in situ forming material may be a multi-arm block copolymer that includes a central core molecule, such as a residue of a polyol, and at least three copolymer arms covalently attached to the central core molecule, each copolymer arm comprising an inner hydrophobic polymer segment covalently attached to the central core molecule and an outer hydrophilic polymer segment covalently attached to the hydrophobic polymer segment, wherein the central core molecule and the hydrophobic polymer segment define a hydrophobic core region (see, e.g., U.S. Pat. No. 6,730,334). The in situ forming material may include a gel-forming macromer that includes at least four polymeric blocks, at least two of which are hydrophobic and at least one of which is hydrophilic, and including a crosslinkable group (see, e.g., U.S. Pat. No. 6,639,014). The in situ forming material may be a water-soluble macromer that includes at least one hydrolysable linkage formed from carbonate or dioxanone groups, at least one water-soluble polymeric block, and at least one polymerizable group (see, e.g., U.S. Pat. No. 6,177,095). The in situ forming material may comprise polyoxyalkylene block copolymers that form weak physical crosslinks to provide gels having a paste-like consistency at physiological temperatures. (see, e.g., U.S. Pat. No. 4,911,926). The in situ forming material may be a thermo-irreversible gel made from polyoxyalkylene polymers and ionic polysaccharides (see, e.g., U.S. Pat. No. 5,126,141). The in situ forming material may be a gel forming composition that includes chitin derivatives (see, e.g., U.S. Pat. No. 5,093,319), chitosan-coagulum (see, e.g., U.S. Pat. No. 4,532,134), or hyaluronic acid (see, e.g., U.S. Pat. No. 4,141,973). The in situ forming material may be an in situ modification of alginate (see, e.g., U.S. Pat. No. 5,266,326). The in situ forming material may be formed from ethylenically unsaturated water soluble macromers that can be crosslinked in contact with tissues, cells, and bioactive molecules to form gels (see, e.g., U.S. Pat. No. 5,573,934). The in situ forming material may include urethane prepolymers used in combination with an unsaturated cyano compound containing a cyano group attached to a carbon atom, such as cyano(meth)acrylic acids and esters thereof (see, e.g., U.S. Pat. No. 4,740,534). The in situ forming material may be a biodegradable hydrogel that polymerizes by a photoinitiated free radical polymerization from water soluble macromers (see, e.g., U.S. Pat. No. 5,410,016). The in situ forming material may be formed from a two component mixture including a first part comprising a serum albumin protein in an aqueous buffer having a pH in a range of about 8.0-11.0, and a second part comprising a water-

compatible or water-soluble bifunctional crosslinking agent. (see, e.g., U.S. Pat. No. 5,583,114).

[0818] In another aspect, in situ forming materials that can be used include those based on the crosslinking of proteins. For example, the in situ forming material may be a biodegradable hydrogel composed of a recombinant or natural human serum albumin and poly(ethylene) glycol polymer solution whereby upon mixing the solution cross-links to form a mechanical non-liquid covering structure which acts as a sealant. See e.g., U.S. Pat. Nos. 6,458,147 and 6,371,975. The in situ forming material may be composed of two separate mixtures based on fibrinogen and thrombin which are dispensed together to form a biological adhesive when intermixed either prior to or on the application site to form a fibrin sealant. See e.g., U.S. Pat. No. 6,764,467. The in situ forming material may be composed of ultrasonically treated collagen and albumin which form a viscous material that develops adhesive properties when crosslinked chemically with glutaraldehyde and amino acids or peptides. See e.g., U.S. Pat. No. 6,310,036. The in situ forming material may be a hydrated adhesive gel composed of an aqueous solution consisting essentially of a protein having amino groups at the side chains (e.g., gelatin, albumin) which is crosslinked with an N-hydroxyimidoester compound. See e.g., U.S. Pat. No. 4,839,345. The in situ forming material may be a hydrogel prepared from a protein or polysaccharide backbone (e.g., albumin or polymannuronic acid) bonded to a cross-linking agent (e.g., polyvalent derivatives of polyethylene or polyalkylene glycol). See e.g., U.S. Pat. No. 5,514,379. The in situ forming material may be composed of a polymerizable collagen composition that is applied to the tissue and then exposed to an initiator to polymerize the collagen to form a seal over a wound opening in the tissue. See e.g., U.S. Pat. No. 5,874,537. The in situ forming material may be a two component mixture composed of a protein (e.g., serum albumin) in an aqueous buffer having a pH in the range of about 8.0-11.0 and a water-soluble bifunctional polyethylene oxide type crosslinking agent, which transforms from a liquid to a strong, flexible bonding composition to seal tissue in situ. See e.g., U.S. Pat. Nos. 5,583,114 and RE38158 and PCT Publication No. WO 96/03159. The in situ forming material may be composed of a protein, a surfactant, and a lipid in a liquid carrier, which is crosslinked by adding a crosslinker and used as a sealant or bonding agent in situ. See e.g., U.S. Patent Application No. 2004/0063613A1 and PCT Publication Nos. WO 01/45761 and WO 03/090683. The in situ forming material may be composed of two enzyme-free liquid components that are mixed by dispensing the components into a catheter tube deployed at the vascular puncture site, wherein, upon mixing, the two liquid components chemically cross-link to form a mechanical non-liquid matrix that seals a vascular puncture site. See e.g., U.S. Patent Application Nos. 2002/0161399A1 and 2001/0018598A1. The in situ forming material may be a cross-linked albumin composition composed of an albumin preparation and a carbodiimide preparation which are mixed under conditions that permit crosslinking of the albumin for use as a bioadhesive or sealant. See e.g., PCT Publication No. WO 99/66964. The in situ forming material may be composed of collagen and a peroxidase and hydrogen peroxide, such that the collagen is crosslinked to from a semi-solid gel that seals a wound. See e.g., PCT Publication No. WO 01/35882.

[0819] In another aspect, in situ forming materials that can be used include those based on isocyanate or isothiocyanate capped polymers. For example, the in situ forming material may be composed of isocyanate-capped polymers that are liquid compositions which form into a solid adhesive coating by in situ polymerization and crosslinking upon contact with body fluid or tissue. See e.g., PCT Publication No. WO 04/021983. The in situ forming material may be a moisture-curing sealant composition composed of an active isocyanato-terminated isocyanate prepolymer containing a polyol component with a molecular weight of 2,000 to 20,000 and an isocyanurating catalyst agent. See e.g., U.S. Pat. No. 5,206,331.

[0820] Representative examples of compositions that undergo electrophilic-nucleophilic crosslinking reactions and methods of preparing such compositions are described in U.S. Pat. Nos. 5,752,974; 5,807,581; 5,874,500; 5,936,035; 6,051,648; 6,165,489; 6,312,725; 6,458,889; 6,495,127; 6,534,591; 6,624,245; 6,566,406; 6,610,033; 6,632,457; U.S. Patent Application Publication No. 2003/0077272; and PCT Application Publication Nos. WO 04/060405 and WO 04/060346. Other examples of in situ forming materials that can be used include those based on the crosslinking of proteins (described in U.S. Pat. Nos. RE38158; 4,839,345; 5,514,379, 5,583,114; 6,458,147; 6,371,975; U.S. Patent Application Publication Nos. 2002/0161399; 2001/0018598 and PCT Publication Nos. WO 03/090683; WO 01/45761; WO 99/66964 and WO 96/03159).

[0821] In another embodiment, the anti-fibrosing (or gliosis-inhibiting) agent can be coated onto the entire device or a portion of the device. In certain embodiments, the agent is present as part of a coating on a surface of the CRM or neurostimulation device, lead and/or electrode. The coating may partially cover or may completely cover the surface of the electrical device, lead and/or electrode. Further, the coating may directly or indirectly contact the electrical device, lead and/or electrode. For example, the CRM or neurostimulation device, lead and/or electrode may be coated with a first coating and then coated with a second coating that includes the anti-scarring (or gliosis-inhibiting) agent.

[0822] CRM and neurostimulation devices, leads and/or electrodes may be coated using a variety of coating methods, including by dipping, spraying, painting, by vacuum deposition, or by any other method known to those of ordinary skill in the art.

[0823] As described above, the anti-fibrosing (or anti-gliotic) agent can be coated onto the appropriate CRM or neurostimulation device, lead and/or electrode using the polymeric coatings described above. In addition to the coating compositions and methods described above, there are various other coating compositions and methods that are known in the art. Representative examples of these coating compositions and methods are described in U.S. Pat. Nos. 6,610,016; 6,358,557; 6,306,176; 6,110,483; 6,106,473; 5,997,517; 5,800,412; 5,525,348; 5,331,027; 5,001,009; 6,562,136; 6,406,754; 6,344,035; 6,254,921; 6,214,901; 6,077,698; 6,603,040; 6,278,018; 6,238,799; 6,096,726, 5,766,158, 5,599,576, 4,119,094; 4,100,309; 6,599,558; 6,369,168; 6,521,283; 6,497,916; 6,251,964; 6,225,431; 6,087,462; 6,083,257; 5,739,237; 5,739,236; 5,705,583; 5,648,442; 5,645,883; 5,556,710; 5,496,581; 4,689,386;

6,214,115; 6,090,901; 6,599,448; 6,054,504; 4,987,182; 4,847,324; and 4,642,267; U.S. Patent Application Publication Nos. 2002/0146581, 2003/0129130, 2001/0026834; 2003/0190420; 2001/0000785; 2003/0059631; 2003/0190405; 2002/0146581; 2003/020399; 2001/0026834; 2003/0190420; 2001/0000785; 2003/0059631; 2003/0190405; and 2003/020399; and PCT Publication Nos. WO 02/055121; WO 01/57048; WO 01/52915; and WO 01/01957.

[0824] In yet another aspect, anti-scarring (or anti-gliosis) agent may be located within pores or voids of the electrical device, lead and/or electrode. For example, a CRM or neurostimulation device, lead and/or electrode may be constructed to have cavities (e.g., divets or holes), grooves, lumen(s), pores, channels, and the like, which form voids or pores in the body of the device, lead and/or electrode. These voids may be filled (partially or completely) with a fibrosis-inhibiting (or gliosis-inhibiting) agent or a composition that comprises a fibrosis-inhibiting (or gliosis-inhibiting) agent.

[0825] Within another aspect of the invention, the biologically active agent can be delivered with non-polymeric agents. These non-polymeric agents can include sucrose derivatives (e.g., sucrose acetate isobutyrate, sucrose oleate), sterols such as cholesterol, stigmasterol, .beta.-sitosterol, and estradiol; cholesteryl esters such as cholesteryl stearate; C_{12}-C_{24} fatty acids such as lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, and lignoceric acid; C_{18}-C_{36} mono-, di- and triacylglycerides such as glyceryl monooleate, glyceryl monolinoleate, glyceryl monolaurate, glyceryl monodocosanoate, glyceryl monomyristate, glyceryl monodicenoate, glyceryl dipalmitate, glyceryl didocosanoate, glyceryl dimyristate, glyceryl didecenoate, glyceryl tridocosanoate, glyceryl trimyristate, glyceryl tridecenoate, glycerol tristearate and mixtures thereof; sucrose fatty acid esters such as sucrose distearate and sucrose palmitate; sorbitan fatty acid esters such as sorbitan monostearate, sorbitan monopalmitate and sorbitan tristearate; C_{16}-C_{18} fatty alcohols such as cetyl alcohol, myristyl alcohol, stearyl alcohol, and cetostearyl alcohol; esters of fatty alcohols and fatty acids such as cetyl palmitate and cetearyl palmitate; anhydrides of fatty acids such as stearic anhydride; phospholipids including phosphatidylcholine (lecithin), phosphatidylserine, phosphatidylethanolamine, phosphatidylinositol, and lysoderivatives thereof; sphingosine and derivatives thereof; spingomyelins such as stearyl, palmitoyl, and tricosanyl spingomyelins; ceramides such as stearyl and palmitoyl ceramides; glycosphingolipids; lanolin and lanolin alcohols, calcium phosphate, sintered and unscintered hydoxyapatite, zeolites, and combinations and mixtures thereof.

[0826] Representative examples of patents relating to non-polymeric delivery systems and their preparation include U.S. Pat. Nos. 5,736,152; 5,888,533; 6,120,789; 5,968,542; and 5,747,058.

[0827] The fibrosis-inhibiting (or gliosis-inhibiting) agent may be delivered as a solution. The fibrosis-inhibiting (or gliosis-inhibiting) agent can be incorporated directly into the solution to provide a homogeneous solution or dispersion. In certain embodiments, the solution is an aqueous solution. The aqueous solution may futher include buffer salts, as well as viscosity modifying agents (e.g., hyaluronic acid, alginates, CMC, and the like). In another aspect of the invention, the solution can include a biocompatible solvent, such as ethanol, DMSO, glycerol, PEG-200, PEG-300 or NMP.

[0828] Within another aspect of the invention, the fibrosis-inhibiting (or gliosis-inhibiting) agent can further comprise a secondary carrier. The secondary carrier can be in the form of microspheres (e.g., PLGA, PLLA, PDLLA, PCL, gelatin, polydioxanone, poly(alkylcyanoacrylate), nanospheres (e.g., PLGA, PLLA, PDLLA, PCL, gelatin, polydioxanone, poly(alkylcyanoacrylate)), liposomes, emulsions, microemulsions, micelles (e.g., SDS, block copolymers of the form X—Y, X—Y—X or Y—X—Y where X is a poly(alkylene oxide) or alkyl ether thereof (e.g., poly(ethylene glycol), methoxy poly(ethylene glycol), poly(propylene glycol), block copolymers of poly(ethylene oxide) and poly(propylene oxide) [e.g., PLURONIC and PLURONIC R polymers (BASF)]) and Y is a polyester where the polyester can comprise the residues of one or more of the monomers selected from lactide, lactic acid, glycolide, glycolic acid, e-caprolactone, gamma-caprolactone, hydroxyvaleric acid, hydroxybutyric acid, beta-butyrolactone, gamma-butyrolactone, gamma-valerolactone, γ-decanolactone, δ-decanolactone, trimethylene carbonate, 1,4-dioxane-2-one or 1,5-dioxepan-2one (e.g., PLGA, PLLA, PDLLA, PCL polydioxanone)), zeolites or cyclodextrins.

[0829] Within another aspect of the invention, these fibrosis-inhibiting (or gliosis-inhibiting) agent/secondary carrier compositions can be a) incorporated directly into, or onto, the CRM or neurostimulation device, lead and/or electrode, b) incorporated into a solution, c) incorporated into a gel or viscous solution, d) incorporated into the composition used for coating the device, lead and/or electrode, or e) incorporated into, or onto, the device, lead and/or electrode following coating of the device, lead and/or electrode with a coating composition.

[0830] For example, fibrosis-inhibiting (or gliosis-inhibiting) agent loaded PLGA microspheres may be incorporated into a polyurethane coating solution which is then coated onto the device, lead and/or electrode.

[0831] In yet another example, the device, lead and/or electrode can be coated with a polyurethane and then allowed to partially dry such that the surface is still tacky. A particulate form of the fibrosis-inhibiting (or gliosis-inhibiting) agent or fibrosis-inhibiting (or gliosis-inhibiting) agent/secondary carrier can then be applied to all or a portion of the tacky coating after which the device is dried.

[0832] In yet another example, the device, lead and/or electrode can be coated with one of the coatings described above. A thermal treatment process can then be used to soften the coating, after which the fibrosis-inhibiting (or gliosis-inhibiting) agent or the fibrosis-inhibiting (or gliosis-inhibiting) agent/secondary carrier is applied to the entire device, lead and/or electrode or to a portion of the device, lead and/or electrode (e.g., outer surface).

[0833] Within another aspect of the invention, the coated CRM or neurostimulation device, lead and/or electrode which inhibits or reduces an in vivo fibrotic (or gliotic) reaction is further coated with a compound or compositions which delay the release of and/or activity of the fibrosis-inhibiting (or gliosis-inhibiting) agent. Representative examples of such agents include biologically inert materials such as gelatin, PLGA/MePEG film, PLA, polyurethanes,

silicone rubbers, surfactants, lipids, or polyethylene glycol, as well as biologically active materials such as heparin or heparin quaternary amine complexes (e.g., heparin-benzalkonium chloride complex) (e.g., to induce coagulation).

[0834] For example, in one embodiment of the invention the active agent on the device, lead and/or electrode is top-coated with a physical barrier. Such barriers can include non-degradable materials or biodegradable materials such as gelatin, PLGA/MePEG film, PLA, or polyethylene glycol among others. In one embodiment, the rate of diffusion of the therapeutic agent in the barrier coat is slower that the rate of diffusion of the therapeutic agent in the coating layer. In the case of PLGA/MePEG, once the PLGA/MePEG becomes exposed to the blood or body fluids, the MePEG may dissolve out of the PLGA, leaving channels through the PLGA to an underlying layer containing the fibrosis-inhibiting (or gliosis-inhibiting) agent, which then can then diffuse into the tissue and initiate its biological activity.

[0835] In another embodiment of the invention, for example, a particulate form of the active agent may be coated onto the CRM or neurostimulation device, lead and/or electrode using a polymer (e.g., PLG, PLA, polyurethane). A second polymer that dissolves slowly or degrades (e.g., MePEG-PLGA or PLG) and that does not contain the active agent may be coated over the first layer. Once the top layer dissolves or degrades, it exposes the under coating which allows the active agent to be exposed to the treatment site or to be released from the coating.

[0836] Within another aspect of the invention, the outer layer of the coating of a coated CRM or neurostimulation device, lead and/or electrode which inhibits an in vivo fibrotic (or gliotic) response is further treated to crosslink the outer layer of the coating. This can be accomplished by subjecting the coated device, lead and/or electrode to a plasma treatment process. The degree of crosslinking and nature of the surface modification can be altered by changing the RF power setting, the location with respect to the plasma, the duration of treatment as well as the gas composition introduced into the plasma chamber.

[0837] Protection of a biologically active surface can also be utilized by coating the CRM or neurostimulator device, lead and/or electrode surface with an inert molecule that prevents access to the active site through steric hindrance, or by coating the surface with an inactive form of the fibrosis-inhibiting (or gliosis-inhibiting) agent, which is later activated. For example, the device, lead and/or electrode can be coated with an enzyme, which causes either release of the fibrosis-inhibiting (or gliosis-inhibiting) agent or activates the fibrosis-inhibiting (or gliosis-inhibiting) agent.

[0838] Another example of a suitable CRM or neurostimulation device, lead and/or electrode surface coating includes an anticoagulant such as heparin or heparin quaternary amine complexes (e.g., heparin-benzalkonium chloride complex), which can be coated on top of the fibrosis-inhibiting (or gliosis-inhibiting) agent; this may also be useful during transvenous placement of pacemaker or ICD leads to prevent clotting. The presence of the anticoagulant delays coagulation. As the anticoagulant dissolves away, the anticoagulant activity may stop, and the newly exposed fibrosis-inhibiting (or gliosis-inhibiting) agent may inhibit or reduce fibrosis (or gliosis) from occurring in the adjacent tissue or coating the device, lead and/or electrode.

[0839] In another aspect, the CRM or neurostimulation device, lead and/or electrode can be coated with an inactive form of the fibrosis-inhibiting (or gliosis-inhibiting) agent, which is then activated once the device is deployed. Such activation may be achieved by injecting another material into the treatment area after the device, lead and/or electrode (as described below) is implanted or after the fibrosis-inhibiting (or gliosis-inhibiting) agent has been administered to the treatment area (via injections, spray, wash, drug delivery catheters or balloons). In this aspect, the device, lead and/or electrode may be coated with an inactive form of the fibrosis-inhibiting (or gliosis-inhibiting) agent. Once the device, lead and/or electrode is implanted, the activating substance is injected or applied into, or onto, the treatment site where the inactive form of the fibrosis-inhibiting (or gliosis-inhibiting) agent has been applied.

[0840] One example of this method includes coating a CRM or neurostimulation device, lead and/or electrode with a biologically active fibrosis-(or gliosis-inhibiting) inhibiting agent, as described herein as described herein. The coating containing the active fibrosis-inhibiting (or gliosis-inhibiting) agent may then be covered with polyethylene glycol and these two substances may then be bonded through an ester bond using a condensation reaction. Prior to the deployment of the device, lead and/or electrode, an esterase is injected into the tissue around the outside of the device (lead or electrode), which can cleave the bond between the ester and the fibrosis-inhibiting (or gliosis-inhibiting) therapeutic agent, allowing the agent to initiate fibrosis (or gliosis) inhibition.

[0841] The devices and compositions of the invention may include one or more additional ingredients and/or therapeutic agents, such as surfactants (e.g., PLURONICS, such as F-127, L-122, L-101, L-92, L-81, and L-61), anti-inflammatory agents (e.g., dexamethasone or aspirin), anti-thrombotic agents (e.g., heparin, high activity heparin, heparin quaternary amine complexes (e.g., heparin benzalkonium chloride complex)), anti-infective agents (e.g., 5-fluorouracil, triclosan, rifamycim, and silver compounds), preservatives, anti-oxidants and/or anti-platelet agents.

[0842] Within certain embodiments of the invention, the device or therapeutic composition can also comprise radio-opaque, echogenic materials and magnetic resonance imaging (MRI) responsive materials (i.e., MRI contrast agents) to aid in visualization of the composition under ultrasound, fluoroscopy and/or MRI. For example, a composition may be echogenic or radiopaque (e.g., made with echogenic or radiopaque with materials such as powdered tantalum, tungsten, barium carbonate, bismuth oxide, barium sulfate, metrazimide, iopamidol, iohexol, iopromide, iobitridol, iomeprol, iopentol, ioversol, ioxilan, iodixanol, iotrolan, acetrizoic acid derivatives, diatrizoic acid derivatives, iothalamic acid derivatives, ioxithalamic acid derivatives, metrizoic acid derivatives, iodamide, lypophylic agents, iodipamide and ioglycamic acid or, by the addition of microspheres or bubbles which present an acoustic interface). For visualization under MRI, contrast agents (e.g., gadolinium (III) chelates or iron oxide compounds) may be incorporated into the composition. In some embodiments, a medical device may include radio-opaque or MRI visible markers (e.g., bands) that may be used to orient and guide the device during the implantation procedure.

[0843] The devices may, alternatively, or in addition, be visualized under visible light, using fluorescence, or by other spectroscopic means. Visualization agents that can be included for this purpose include dyes, pigments, and other colored agents. In one aspect, the composition may further include a colorant to improve visualization of the composition in vivo and/or ex vivo. Frequently, compositions can be difficult to visualize upon delivery into a host, especially at the margins of an implant or tissue. A coloring agent can be incorporated into a composition to reduce or eliminate the incidence or severity of this problem. The coloring agent provides a unique color, increased contrast, or unique fluorescence characteristics to the composition. In one aspect, a composition is provided that includes a colorant such that it is readily visible (under visible light or using a fluorescence technique) and easily differentiated from its implant site. In another aspect, a colorant can be included in a liquid or semi-solid composition. For example, a single component of a two component mixture may be colored, such that when combined ex-vivo or in-vivo, the mixture is sufficiently colored.

[0844] The coloring agent may be, for example, an endogenous compound (e.g., an amino acid or vitamin) or a nutrient or food material and may be a hydrophobic or a hydrophilic compound. Preferably, the colorant has a very low or no toxicity at the concentration used. Also preferred are colorants that are safe and normally enter the body through absorption such as β-carotene. Representative examples of colored nutrients (under visible light) include fat soluble vitamins such as Vitamin A (yellow); water soluble vitamins such as Vitamin B12 (pink-red) and folic acid (yellow-orange); carotenoids such as β-carotene (yellow-purple) and lycopene (red). Other examples of coloring agents include natural product (berry and fruit) extracts such as anthrocyanin (purple) and saffron extract (dark red). The coloring agent may be a fluorescent or phosphorescent compound such as α-tocopherolquinol (a Vitamin E derivative) or L-tryptophan.

[0845] In one aspect, the devices and compositions of the present invention include one or more coloring agents, also referred to as dyestuffs, which may be present in an effective amount to impart observable coloration to the composition, e.g., the gel. Examples of coloring agents include dyes suitable for food such as those known as F. D. & C. dyes and natural coloring agents such as grape skin extract, beet red powder, beta carotene, annato, carmine, turmeric, paprika, and so forth. Derivatives, analogues, and isomers of any of the above colored compound also may be used. The method for incorporating a colorant into an implant or therapeutic composition may be varied depending on the properties of and the desired location for the colorant. For example, a hydrophobic colorant may be selected for hydrophobic matrices. The colorant may be incorporated into a carrier matrix, such as micelles. Further, the pH of the environment may be controlled to further control the color and intensity.

[0846] In one aspect, the devices compositions of the present invention include one or more preservatives or bacteriostatic agents present in an effective amount to preserve the composition and/or inhibit bacterial growth in the composition, for example, bismuth tribromophenate, methyl hydroxybenzoate, bacitracin, ethyl hydroxybenzoate, propyl hydroxybenzoate, erythromycin, chlorocresol, benzalkonium chlorides, and the like. Examples of the preservative include paraoxybenzoic acid esters, chlorobutanol, benzylalcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid, etc. In one aspect, the compositions of the present invention include one or more bactericidal (also known as bacteriacidal) agents.

[0847] In one aspect, the devices and compositions of the present invention include one or more antioxidants, present in an effective amount. Examples of the antioxidant include sulfites, alpha-tocopherol and ascorbic acid.

[0848] Within certain aspects of the present invention, the therapeutic composition should be biocompatible, and release one or more fibrosis-inhibiting agents over a period of several hours, days, or, months. As described above, "release of an agent" refers to any statistically significant presence of the agent, or a subcomponent thereof, which has disassociated from the compositions and/or remains active on the surface of (or within) the composition. The compositions of the present invention may release the anti-scarring agent at one or more phases, the one or more phases having similar or different performance (e.g., release) profiles. The therapeutic agent may be made available to the tissue at amounts which may be sustainable, intermittent, or continuous; in one or more phases; and/or rates of delivery; effective to reduce or inhibit any one or more components of fibrosis (or scarring) (or gliosis), including: formation of new blood vessels (angiogenesis), migration and proliferation of connective tissue cells (such as fibroblasts or smooth muscle cells), deposition of extracellular matrix (ECM), and remodeling (maturation and organization of the fibrous tissue).

[0849] Thus, release rate may be programmed to impact fibrosis (or scarring) by releasing an anti-scarring agent at a time such that at least one of the components of fibrosis (or gliosis) is inhibited or reduced. Moreover, the predetermined release rate may reduce agent loading and/or concentration as well as potentially providing minimal drug washout and thus, increases efficiency of drug effect. Any one of the anti-scarring agents described herein may perform one or more functions, including inhibiting the formation of new blood vessels (angiogenesis), inhibiting the migration and proliferation of connective tissue cells (such as fibroblasts or smooth muscle cells), inhibiting the deposition of extracellular matrix (ECM), and inhibiting remodeling (maturation and organization of the fibrous tissue). In one embodiment, the rate of release may provide a sustainable level of the anti-scarring agent to the susceptible tissue site. In another embodiment, the rate of release is substantially constant. The rate may decrease and/or increase over time, and it may optionally include a substantially non-release period. The release rate may comprise a plurality of rates. In an embodiment, the plurality of release rates may include rates selected from the group consisting of substantially constant, decreasing, increasing, and substantially non-releasing.

[0850] The total amount of anti-scarring agent made available on, in or near the device may be in an amount ranging from about 0.01 μg (micrograms) to about 2500 mg (milligrams). Generally, the anti-scarring agent may be in the amount ranging from 0.01 μg to about 10 μg; or from 10 μg to about 1 mg; or from 1 mg to about 10 mg; or from 10 mg to about 100 mg; or from 100 mg to about 500 mg; or from 500 mg to about 2500 mg.

[0851] The surface amount of anti-scarring agent on, in or near the device may be in an amount ranging from less than

0.01 μg to about 250 μg per mm^2 of device surface area. Generally, the anti-scarring agent may be in the amount ranging from less than 0.01 μg per mm^2; or from 0.01 μg to about 10 μg per mm^2; or from 10 μg to about 250 μg per mm^2.

[0852] The anti-scarring agent that is on, in or near the device may be released from the composition in a time period that may be measured from the time of implantation, which ranges from about less than 1 day to about 180 days. Generally, the release time may also be from about less than 1 day to about 7 days; from 7 days to about 14 days; from 14 days to about 28 days; from 28 days to about 56 days; from 56 days to about 90 days; from 90 days to about 180 days.

[0853] The amount of anti-scarring agent released from the composition as a function of time may be determined based on the in vitro release characteristics of the agent from the composition. The in vitro release rate may be determined by placing the anti-scarring agent within the composition or device in an appropriate buffer such as 0.1M phosphate buffer (pH 7.4)) at 37° C. Samples of the buffer solution are then periodically removed for analysis by HPLC, and the buffer is replaced to avoid any saturation effects.

[0854] Based on the in vitro release rates, the release of anti-scarring agent per day may range from an amount ranging from about 0.01 μg (micrograms) to about 2500 mg (milligrams). Generally, the anti-scarring agent that may be released in a day may be in the amount ranging from 0.01 μg to about 10 μg; or from 10 μg to about 1 mg; or from 1 mg to about 10 mg; or from 10 mg to about 100 mg; or from 100 mg to about 500 mg; or from 500 mg to about 2500 mg.

[0855] In one embodiment, the anti-scarring agent is made available to the susceptible tissue site in a programmed, sustained, and/or controlled manner which results in increased efficiency and/or efficacy. Further, the release rates may vary during either or both of the initial and subsequent release phases. There may also be additional phase(s) for release of the same substance(s) and/or different substance(s).

[0856] Further, therapeutic compositions and devices of the present invention should preferably have a stable shelf-life of at least several months and be capable of being produced and maintained under sterile conditions. Many pharmaceuticals are manufactured to be sterile and this criterion is defined by the USP XXII <1211>. The term "USP" refers to U.S. Pharmacopeia (see www.usp.org, Rockville, Md.). Sterilization may be accomplished by a number of means accepted in the industry and listed in the USP XXII <1211>, including gas sterilization, ionizing radiation or, when appropriate, filtration. Sterilization may be maintained by what is termed asceptic processing, defined also in USP XXII <1211>. Acceptable gases used for gas sterilization include ethylene oxide. Acceptable radiation types used for ionizing radiation methods include gamma, for instance from a cobalt 60 source and electron beam. A typical dose of gamma radiation is 2.5 MRad. Filtration may be accomplished using a filter with suitable pore size, for example 0.22 μm and of a suitable material, for instance polytetrafluoroethylene (e.g., TEFLON from E.I. DuPont De Nemours and Company, Wilmington, Del.).

[0857] In another aspect, the compositions and devices of the present invention are contained in a container that allows them to be used for their intended purpose, i.e., as a pharmaceutical composition. Properties of the container that are important are a volume of empty space to allow for the addition of a constitution medium, such as water or other aqueous medium, e.g., saline, acceptable light transmission characteristics in order to prevent light energy from damaging the composition in the container (refer to USP XXII <661>), an acceptable limit of extractables within the container material (refer to USP XXII), an acceptable barrier capacity for moisture (refer to USP XXII <671>) or oxygen. In the case of oxygen penetration, this may be controlled by including in the container, a positive pressure of an inert gas, such as high purity nitrogen, or a noble gas, such as argon.

[0858] Typical materials used to make containers for pharmaceuticals include USP Type I through III and Type NP glass (refer to USP XXII <661>), polyethylene, TEFLON, silicone, and gray-butyl rubber.

[0859] In one embodiment, the product containers can be thermoformed plastics. In another embodiment, a secondary package can be used for the product. In another embodiment, product can be in a sterile container that is placed in a box that is labeled to describe the contents of the box.

[0860] 1) Coating of CRM or Neurostimulation Devices, Leads and Electrodes with Fibrosis-Inhibiting (or Gliosis-Inhibiting) Agents

[0861] As described above, a range of polymeric and non-polymeric materials can be used to incorporate the fibrosis-inhibiting (or gliosis-inhibiting) agent onto or into an electrical device, lead or electrode. Coating the device, lead and/or electrode with these fibrosis-inhibiting (or gliosis-inhibiting) agent-containing compositions, or with the fibrosis-inhibiting (or gliosis-inhibiting) agent only, is one process that can be used to incorporate the fibrosis-inhibiting (or gliosis-inhibiting) agent into or onto the device, lead and/or electrode.

[0862] a) Dip Coating

[0863] Dip coating is an example of coating process that can be used to associate the anti-scarring (or gliosis-inhibiting) agent with the device, lead and/or electrode. In one embodiment, the fibrosis-inhibiting (or gliosis-inhibiting) agent is dissolved in a solvent for the fibrosis-inhibiting (or gliosis-inhibiting) agent and is then coated onto the device, lead and/or electrode.

[0864] Fibrosis-Inhibiting (or Gliosis-Inhibiting) Agent with an Inert Solvent

[0865] In one embodiment, the solvent is an inert solvent for the device, lead or electrode such that the solvent does not dissolve the medical device, lead or electrode to any great extent and is not absorbed by the device, lead or electrode to any great extent. The device, lead or electrode can be immersed, either partially or completely, in the fibrosis-inhibiting (or gliosis-inhibiting) agent/solvent solution for a specific period of time. The rate of immersion into the fibrosis-inhibiting (or gliosis-inhibiting) agent/solvent solution can be altered (e.g., 0.001 cm per sec to 50 cm per sec). The device, lead and/or electrode can then be removed from the solution. The rate at which the device, lead or electrode is withdrawn from the solution can be altered (e.g., 0.001 cm per sec to 50 cm per sec). The coated device, lead or electrode can be air-dried. The dipping process can be

repeated one or more times depending on the specific application, where higher repetitions generally increase the amount of agent that is coated onto the device, lead or electrode. The device, lead or electrode can be dried under vacuum to reduce residual solvent levels. This process may result in the fibrosis-inhibiting (or gliosis-inhibiting) agent being coated on the surface of the device.

[0866] Fibrosis-Inhibiting (or Gliosis-Inhibiting) Agent with a Swelling Solvent

[0867] In one embodiment, the solvent is one that will not dissolve the CRM or neurostimulation device, lead or electrode but will be absorbed by the device, lead or electrode. In certain cases, these solvents can swell the device, lead or electrode to some extent. The device, lead or electrode can be immersed, either partially or completely, in the fibrosis-inhibiting (or gliosis-inhibiting) agent/solvent solution for a specific period of time (seconds to days). The rate of immersion into the fibrosis-inhibiting (or gliosis-inhibiting) agent/solvent solution can be altered (e.g., 0.001 cm per sec to 50 cm per sec). The device, lead and/or electrode can then be removed from the solution. The rate at which the device, lead or electrode is withdrawn from the solution can be altered (e.g., 0.001 cm per sec to 50 cm per sec). The coated device, lead or electrode can be air-dried. The dipping process can be repeated one or more times depending on the specific application. The device, lead or electrode can be dried under vacuum to reduce residual solvent levels. This process results in the fibrosis-inhibiting (or gliosis-inhibiting) agent being adsorbed into the CRM or neurostimulation device, lead or electrode. The fibrosis-inhibiting (or gliosis-inhibiting) agent may also be present on the surface of the device, lead and/or electrode. The amount of surface associated fibrosis-inhibiting (or gliosis-inhibiting) agent may be reduced by dipping the coated device, lead or electrode into a solvent for the fibrosis-inhibiting (or gliosis-inhibiting) agent, or by spraying the coated device, lead or electrode with a solvent for the fibrosis-inhibiting (or gliosis-inhibiting) agent.

[0868] Fibrosis-Inhibiting (or Gliosis-Inhibiting) Agent with a Solvent

[0869] In one embodiment, the solvent is one that may be absorbed by the device, lead or electrode and that will dissolve the device, lead or electrode. The device, lead or electrode can be immersed, either partially or completely, in the fibrosis-inhibiting (or gliosis-inhibiting) agent/solvent solution for a specific period of time (seconds to hours). The rate of immersion into the fibrosis-inhibiting (or gliosis-inhibiting) agent/solvent solution can be altered (e.g., 0.001 cm per sec to 50 cm per sec). The device, lead or electrode can then be removed from the solution. The rate at which the device, lead or electrode is withdrawn from the solution can be altered (e.g., 0.001 cm per sec to 50 cm per sec). The coated device, lead or electrode can be air-dried. The dipping process can be repeated one or more times depending on the specific application. The device, lead or electrode can be dried under vacuum to reduce residual solvent levels. This process will result in the fibrosis-inhibiting (or gliosis-inhibiting) agent being adsorbed into the medical device, lead or electrode as well as being surface associated. The exposure time of the device, lead or electrode to the solvent should not incur significant permanent dimensional changes to the device, lead or electrode. The fibrosis-inhibiting (or gliosis-inhibiting) agent may also be present on the surface of the device, lead or electrode. The amount of surface associated fibrosis-inhibiting (or gliosis-inhibiting) agent may be reduced by dipping the coated device, lead or electrode into a solvent for the fibrosis-inhibiting (or gliosis-inhibiting) agent or by spraying the coated device, lead or electrode with a solvent for the fibrosis-inhibiting (or gliosis-inhibiting) agent.

[0870] In one embodiment, the fibrosis-inhibiting (or gliosis-inhibiting) agent and a polymer are dissolved in a solvent, for both the polymer and the fibrosis-inhibiting (or gliosis-inhibiting) agent, and are then coated onto the device, lead or electrode.

[0871] In the above description the device, lead or electrode can be one that has not been modified or one that has been further modified by coating with a polymer, surface treated by plasma treatment, flame treatment, corona treatment, surface oxidation or reduction, surface etching, mechanical smoothing or roughening, or grafting prior to the coating process.

[0872] In any one the above dip coating methods, the surface of the device, lead or electrode can be treated with a plasma polymerization method prior to coating of the fibrosis-inhibiting (or gliosis-inhibiting) agent or fibrosis-inhibiting (or gliosis-inhibiting) agent-containing composition, such that a thin polymeric layer is deposited onto the device, lead or electrode surface. Examples of such methods include parylene coating of devices and the use of various monomers such hydrocyclosiloxane monomers. Parylene coating may be especially advantageous if the device, or portions of the device (such as the lead or the electrode), are composed of materials (e.g., stainless steel, nitinol) that do not allow incorporation of the therapeutic agent(s) into the surface layer using one of the above methods. A parylene primer layer may be deposited onto the electrical device, lead or electrode using a parylene coater (e.g., PDS 2010 LABCOATER2 from Cookson Electronics) and a suitable reagent (e.g., di-p-xylylene or dichloro-di-p-xylylene) as the coating feed material. Parylene compounds are commercially available, for example, from Specialty Coating Systems, Indianapolis, Ind.), including PARYLENE N (di-p-xylylene), PARYLENE C (a monchlorinated derivative of PARYLENE N, and Parylene D, a dichlorinated derivative of PARYLENE N).

[0873] b) Spray Coating CRM and Neurostimulation Devices, Leads and Electrodes

[0874] Spray coating is another coating process that can be used. In the spray coating process, a solution or suspension of the fibrosis-inhibiting (or gliosis-inhibiting) agent, with or without a polymeric or non-polymeric carrier, is nebulized and directed to the device, lead and/or electrode to be coated by a stream of gas. One can use spray devices such as an air-brush (for example models 2020, 360, 175, 100, 200, 150, 350, 250, 400, 3000, 4000, 5000, 6000 from Badger Air-brush Company, Franklin Park, Ill.), spray painting equipment, TLC reagent sprayers (for example Part # 14545 and 14654, Alltech Associates, Inc. Deerfield, Ill., and ultrasonic spray devices (for example those available from Sono-Tek, Milton, N.Y.). One can also use powder sprayers and electrostatic sprayers.

[0875] In one embodiment, the fibrosis-inhibiting (or gliosis-inhibiting) agent is dissolved in a solvent for the fibrosis agent and is then sprayed onto the device, lead and/or electrode.

[0876] Fibrosis-Inhibiting (or Gliosis-Inhibiting) Agent with an Inert Solvent

[0877] In one embodiment, the solvent is an inert solvent for the device, lead or electrode such that the solvent does not dissolve the medical device, lead or electrode to any great extent and is not absorbed to any great extent. The device, lead or electrode can be held in place or mounted onto a mandrel or rod that has the ability to move in an X, Y or Z plane or a combination of these planes. Using one of the above described spray devices, the device, lead or electrode can be spray coated such that it is either partially or completely coated with the fibrosis-inhibiting (or gliosis-inhibiting) agent/solvent solution. The rate of spraying of the fibrosis-inhibiting (or gliosis-inhibiting) agent/solvent solution can be altered (e.g., 0.001 mL per sec to 10 mL per sec) to ensure that a good coating of the fibrosis-inhibiting (or gliosis-inhibiting) agent is obtained. The coated device, lead or electrode can be air-dried. The spray coating process can be repeated one or more times depending on the specific application. The device, lead or electrode can be dried under vacuum to reduce residual solvent levels. This process results in the fibrosis-inhibiting (or gliosis-inhibiting) agent being coated on the surface of the device, lead and/or electrode.

[0878] Fibrosis-Inhibiting (or Gliosis-Inhibiting) Agent with a Swelling Solvent

[0879] In one embodiment, the solvent is one that will not dissolve the device, lead or electrode but will be absorbed by it. These solvents can thus swell the device, lead or electrode to some extent. The device, lead or electrode can be spray coated, either partially or completely, in the fibrosis-inhibiting (or gliosis-inhibiting) agent/solvent solution. The rate of spraying of the fibrosis-inhibiting (or gliosis-inhibiting) agent/solvent solution can be altered (e.g., 0.001 mL per sec to 10 mL per sec) to ensure that a good coating of the fibrosis-inhibiting (or gliosis-inhibiting) agent is obtained. The coated device, lead or electrode can be air-dried. The spray coating process can be repeated one or more times depending on the specific application. The device, lead or electrode can be dried under vacuum to reduce residual solvent levels. This process can result in the fibrosis-inhibiting (or gliosis-inhibiting) agent being adsorbed into the medical device, lead or electrode. The fibrosis-inhibiting (or gliosis-inhibiting) agent may also be present on the surface of the device, lead or electrode. The amount of surface associated fibrosis-inhibiting (or gliosis-inhibiting) agent may be reduced by dipping the coated device, lead or electrode into a solvent for the fibrosis-inhibiting (or gliosis-inhibiting) agent, or by spraying the coated device, lead or electrode with a solvent for the fibrosis-inhibiting (or gliosis-inhibiting) agent.

[0880] Fibrosis-Inhibiting (or Gliosis-Inhibiting) Agent with a Solvent

[0881] In one embodiment, the solvent is one that will be absorbed by the device, lead or electrode and that will dissolve it. The device, lead or electrode can be spray coated, either partially or completely, in the fibrosis-inhibiting (or gliosis-inhibiting) agent/solvent solution. The rate of spraying of the fibrosis-inhibiting (or gliosis-inhibiting) agent/solvent solution can be altered (e.g., 0.001 mL per sec to 10 mL per sec) to ensure that a good coating of the fibrosis-inhibiting (or gliosis-inhibiting) agent is obtained. The coated device, lead or electrode can be air-dried. The spray coating process can be repeated one or more times depending on the specific application. The device, lead or electrode can be dried under vacuum to reduce residual solvent levels. This process will result in the fibrosis-inhibiting (or gliosis-inhibiting) agent being adsorbed into the medical device, lead or electrode as well as being surface associated. In one embodiment, the exposure time of the device, lead or electrode to the solvent may not incur significant permanent dimensional changes to it. The fibrosis-inhibiting (or gliosis-inhibiting) agent may also be present on the surface of the device, lead or electrode. The amount of surface associated fibrosis-inhibiting (or gliosis-inhibiting) agent may be reduced by dipping the coated device, lead or electrode into a solvent for the fibrosis-inhibiting (or gliosis-inhibiting) agent, or by spraying the coated device, lead or electrode with a solvent for the fibrosis-inhibiting (or gliosis-inhibiting) agent.

[0882] In the above description the device, lead or electrode can be one that has not been modified as well as one that has been further modified by coating with a polymer (e.g., parylene), surface treated by plasma treatment, flame treatment, corona treatment, surface oxidation or reduction, surface etching, mechanical smoothing or roughening, or grafting prior to the coating process.

[0883] In one embodiment, the fibrosis-inhibiting (or gliosis-inhibiting) agent and a polymer are dissolved in a solvent, for both the polymer and the anti-fibrosing (or gliosis-inhibiting) agent, and are then spray coated onto the device, lead or electrode.

[0884] Fibrosis-Inhibiting (or Gliosis-Inhibiting) Agent/Polymer with an Inert Solvent

[0885] In one embodiment, the solvent is an inert solvent for the device, lead or electrode such that the solvent does not dissolve it to any great extent and is not absorbed by it to any great extent. The device, lead or electrode can be spray coated, either partially or completely, in the fibrosis-inhibiting (or gliosis-inhibiting) agent/polymer/solvent solution for a specific period of time. The rate of spraying of the fibrosis-inhibiting (or gliosis-inhibiting) agent/solvent solution can be altered (e.g., 0.001 mL per sec to 10 mL per sec) to ensure that a good coating of the fibrosis-inhibiting (or gliosis-inhibiting) agent is obtained. The coated device, lead or electrode can be air-dried. The spray coating process can be repeated one or more times depending on the specific application. The device, lead or electrode can be dried under vacuum to reduce residual solvent levels. This process can result in the fibrosis-inhibiting (or gliosis-inhibiting) agent/polymer being coated on the surface of the device, lead or electrode.

[0886] Fibrosis-Inhibiting (or Gliosis-Inhibiting) Agent/Polymer with a Swelling Solvent

[0887] In one embodiment, the solvent is one that will not dissolve the device, lead or electrode but will be absorbed by it. These solvents can thus swell the device, lead or electrode to some extent. The device, lead or electrode can be spray

coated, either partially or completely, in the fibrosis-inhibiting (or gliosis-inhibiting) agent/polymer/solvent solution. The rate of spraying of the fibrosis-inhibiting (or gliosis-inhibiting) agent/solvent solution can be altered (e.g., 0.001 mL per sec to 10 mL per sec) to ensure that a good coating of the fibrosis-inhibiting (or gliosis-inhibiting) agent is obtained. The coated device, lead or electrode can be air-dried. The spray coating process can be repeated one or more times depending on the specific application. The device, lead or electrode can be dried under vacuum to reduce residual solvent levels. This process will result in the fibrosis-inhibiting (or gliosis-inhibiting) agent/polymer being coated onto the surface of the device, lead or electrode as well as the potential for the fibrosis-inhibiting (or gliosis-inhibiting) agent being adsorbed into the medical device, lead or electrode. The fibrosis-inhibiting (or gliosis-inhibiting) agent may also be present on the surface of the device, lead or electrode. The amount of surface associated fibrosis-inhibiting (or gliosis-inhibiting) agent may be reduced by dipping the coated device, lead or electrode into a solvent for the fibrosis-inhibiting (or gliosis-inhibiting) agent or by spraying the coated device, lead or electrode with a solvent for the fibrosis-inhibiting (or gliosis-inhibiting) agent.

[0888] Fibrosis-Inhibiting (or Gliosis-Inhibiting) Agent/Polymer with a Solvent

[0889] In one embodiment, the solvent is one that will be absorbed by the device, lead or electrode and that will dissolve it. The device, lead or electrode can be spray coated, either partially or completely, in the fibrosis-inhibiting (or gliosis-inhibiting) agent/solvent solution. The rate of spraying of the fibrosis-inhibiting (or gliosis-inhibiting) agent/solvent solution can be altered (e.g., 0.001 mL per sec to 10 mL per sec) to ensure that a good coating of the fibrosis-inhibiting (or gliosis-inhibiting) agent is obtained. The coated device, lead or electrode can be air-dried. The spray coating process can be repeated one or more times depending on the specific application. The device, lead or electrode can be dried under vacuum to reduce residual solvent levels. In the preferred embodiment, the exposure time of the device, lead or electrode to the solvent may not incur significant permanent dimensional changes to it (other than those associated with the coating itself). The fibrosis-inhibiting (or gliosis-inhibiting) agent may also be present on the surface of the device, lead or electrode. The amount of surface associated fibrosis-inhibiting (or gliosis-inhibiting) agent may be reduced by dipping the coated device, lead or electrode into a solvent for the fibrosis-inhibiting (or gliosis-inhibiting) agent or by spraying the coated device, lead or electrode with a solvent for the fibrosis-inhibiting (or gliosis-inhibiting) agent.

[0890] In the above description the device, lead or electrode can be one that has not been modified as well as one that has been further modified by coating with a polymer (e.g., parylene), surface treated by plasma treatment, flame treatment, corona treatment, surface oxidation or reduction, surface etching, mechanical smoothing or roughening, or grafting prior to the coating process.

[0891] In another embodiment, a suspension of the fibrosis-inhibiting (or gliosis-inhibiting) agent in a polymer solution can be prepared. The suspension can be prepared by choosing a solvent that can dissolve the polymer but not the fibrosis-inhibiting (or gliosis-inhibiting) agent, or a solvent that can dissolve the polymer and in which the fibrosis-inhibiting (or gliosis-inhibiting) agent is above its solubility limit. In similar processes described above, the suspension of the fibrosis-inhibiting (or gliosis-inhibiting) and polymer solution can be sprayed onto the CRM or neurostimulation device, lead or electrode such that it is coated with a polymer that has a fibrosis-inhibiting (or gliosis-inhibiting) agent suspended within it.

[0892] The present invention, in various aspects and embodiments, provides the following medical devices:

[0893] 1. Electrical Device

[0894] In one aspect, the present invention provides a medical device, comprising an electrical device and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the medical device and the host into which the medical device is implanted.

[0895] Such a medical device may be defined by one, two, or more of the following features: the electrical device is a neurostimulator; the electrical device is a spinal cord stimulator; the electrical device is a brain stimulator; the electrical device is a vagus nerve stimulator; the electrical device is a sacral nerve stimulator; the electrical device is a gastric nerve stimulator; the electrical device is an auditory nerve stimulator; the electrical device delivers stimulation to organs; the electrical device delivers stimulation to bone; the electrical device delivers stimulation to muscles; the electrical device delivers stimulation to tissues; the electrical device is a device for continuous subarachnoid infusion; the electrical device is an implantable electrode; the electrical device is an implantable pulse generator; the electrical device is an electrical lead; the electrical device is a stimulation lead; the electrical device is a simulation catheter lead; the electrical device is cochlear implant; the electrical device is a microstimulator; the electrical device is battery powered; the electrical device is radio frequency powered; the electrical device is both battery and radio frequency powered; the electrical device is a cardiac rhythm management device; the electrical device is a cardiac pacemaker; the electrical device is an implantable cardioverter defibrillator system; the electrical device is a cardiac lead; the electrical device is a pacer lead; the electrical device is an endocardial lead; the electrical device is a cardioversion/defibrillator lead; the electrical device is an epicardial lead; the electrical device is an epicardial defibrillator lead; the electrical device is a patch defibrillator; the electrical device is a patch defibrillator lead; the electrical device is an electrical patch; the electrical device is a transvenous lead; the electrical device is an active fixation lead; the electrical device is a passive fixation lead; the electrical device is a sensing lead; the electrical device is a defibrillator; the electrical device is an implantable sensor; the electrical device is a left ventricular assist device; the electrical device is a pulse generator; the electrical device is a patch lead; the electrical device is an electrical patch; the electrical device is a cardiac stimulator; the electrical device is an electrical deviceable sensor; the electrical device is an electrical deviceable pump; the electrical device is a dural patch; the electrical device is a ventricular peritoneal shunt; the electrical device is a ventricular atrial shunt; the electrical device is adapted for treating or preventing epidural fibrosis post-laminectomy; the electrical device is adapted for treating or pre-

venting cardiac rhythm abnormalities; the electrical device is adapted for treating or preventing atrial rhythm abnormalities; the electrical device is adapted for treating or preventing conduction abnormalities; the electrical device is adapted for treating or preventing ventricular rhythm abnormalities; the electrical device is adapted for treating or preventing pain; the electrical device is adapted for treating or preventing epilepsy; the electrical device is adapted for treating or preventing Parkinson's disease; the electrical device is adapted for treating or preventing movement disorders; the electrical device is adapted for treating or preventing obesity; the electrical device is adapted for treating or preventing depression; the electrical device is adapted for treating or preventing anxiety; the electrical device is adapted for treating or preventing hearing loss; the electrical device is adapted for treating or preventing ulcers; the electrical device is adapted for treating or preventing deep vein thrombosis; the electrical device is adapted for treating or preventing muscular atrophy; the electrical device is adapted for treating or preventing joint stiffness; the electrical device is adapted for treating or preventing muscle spasms; the electrical device is adapted for treating or preventing osteoporosis; the electrical device is adapted for treating or preventing scoliosis; the electrical device is adapted for treating or preventing spinal disc degeneration; the electrical device is adapted for treating or preventing spinal cord injury; the electrical device is adapted for treating or preventing urinary dysfunction; the electrical device is adapted for treating or preventing gastroparesis; the electrical device is adapted for treating or preventing malignancy; the electrical device is adapted for treating or preventing arachnoiditis; the electrical device is adapted for treating or preventing chronic disease; the electrical device is adapted for treating or preventing migraine; the electrical device is adapted for treating or preventing sleep disorders; the electrical device is adapted for treating or preventing dementia; and the electrical device is adapted for treating or preventing Alzheimer's disease.

[0896] 2. Neurostimulator for Treating Chronic Pain

[0897] In one aspect, the present invention provides a medical device, comprising a neurostimulator for treating chronic pain (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the medical device and the host into which the medical device is implanted.

[0898] Such a medical device may be further defined by one, two, or more of the following features: the chronic pain results from injury; the chronic pain results from an illness; the chronic pain results from scoliosis; the chronic pain results from spinal disc degeneration; the chronic pain results from malignancy; the chronic pain results from arachnoiditis; the chronic pain results from a chronic disease; the chronic pain results from a pain syndrome; the neurostimulator comprises a lead that delivers electrical stimulation to a nerve and an electrical connection that connects a power source to the lead; the neurostimulator is adapted for spinal cord stimulation, and comprises a sensor that detects the position of the spine and a stimulator that emits pulses that decrease in amplitude when the back is in a supine position; the neurostimulator comprises an electrode and a control circuit that generates pulses and rest period based on intervals corresponding to the host body's activity and regeneration period; the neurostimulator comprises a stimulation catheter lead and an electrode; and the neurostimulator is a self-centering epidural spinal cord lead.

[0899] 3. Neurostimulator for Treating Parkinson's Disease

[0900] In one aspect, the present invention provides a medical device, comprising a neurostimulator for treating Parkinson's Disease (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the medical device and the host into which the medical device is implanted.

[0901] In certain embodiments, the neurostimulator comprises an intracranially implantable electrical control module and an electrode. In other embodiments, the neurostimulator comprises a sensor and an electrode.

[0902] 4. Vagal Nerve Stimulator for Treating Epilepsy

[0903] In one aspect, the present invention provides a medical device, comprising a vagal nerve stimulator for treating epilepsy (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the medical device and the host into which the medical device is implanted.

[0904] 5. Vagal Nerve Stimulator for Treating Other Disorders

[0905] In one aspect, the present invention provides a medical device, comprising a vagal nerve stimulator (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the medical device and the host into which the medical device is implanted. Such a medical device may be further defined by one, two or more of the following features: the vagal nerve stimulator is adapted for treating or preventing depression; the vagal nerve stimulator is adapted for treating or preventing anxiety; the vagal nerve stimulator is adapted for treating or preventing panic disorders; the vagal nerve stimulator is adapted for treating or preventing obsessive-compulsive disorders; the vagal nerve stimulator is adapted for treating or preventing post-traumatic disorders; the vagal nerve stimulator is adapted for treating or preventing obesity; the vagal nerve stimulator is adapted for treating or preventing migraine; the vagal nerve stimulator is adapted for treating or preventing sleep disorders; the vagal nerve stimulator is adapted for treating or preventing dementia; the vagal nerve stimulator is adapted for treating or preventing Alzheimer's disease; and the vagal nerve stimulator is adapted for treating or preventing chronic or degenerative neurological disorders.

[0906] 6. Sacral Nerve Stimulator

[0907] In one aspect, the present invention provides a medical device, comprising a sacral nerve stimulator for treating a bladder control problem (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the medical device and the host into which the medical device is implanted.

[0908] Such a medical device may be further defined by one, two, or more of the following features: the sacral nerve

stimulator is adapted for treating or preventing urge incontinence; the sacral nerve stimulator is adapted for treating or preventing nonobstructive urinary retention; the sacral nerve stimulator is adapted for treating or preventing urgency frequency; the sacral nerve stimulator is an intramuscular electrical stimulator; and the sacral nerve stimulator is a leadless, tubular-shaped microstimulator.

[0909] 7. Gastric Nerve Stimulator

[0910] In one aspect, the present invention provides a medical device, comprising a gastric nerve stimulator for treating a gastrointestinal disorder (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the medical device and the host into which the medical device is implanted.

[0911] Such a medical device may be further defined by one, two, or more of the following features: the gastric nerve stimulator is adapted for treating or preventing morbid obesity; the gastric nerve stimulator is adapted for treating or preventing constipation; the gastric nerve stimulator comprises an electrical lead, an electrode and a stimulation generator; and the gastric nerve stimulator comprises an electrical signal controller, connector wire and an attachment lead.

[0912] 8. Cochlear Implant

[0913] The present invention provides a medical device, comprising a cochlear implant for treating deafness (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the medical device and the host into which the medical device is implanted.

[0914] Such a medical device may be further defined by one, two or more the following features: the cochlear implant comprises a plurality of transducer elements; the cochlear implant comprises a sound-to-electrical stimulation encoder, a body implantable receiver-stimulator, and electrodes; the cochlear implant comprises a transducer and an electrode array; and the cochlear implant is a subcranially implantable electomechanical system.

[0915] 9. Bone Growth Stimulator

[0916] In one aspect, the present invention provides a medical device, comprising a bone growth stimulator (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the medical device and the host into which the medical device is implanted.

[0917] In certain embodiments, the bone growth stimulator comprises an electrode and a generator having a strain response piezoelectric material that responds to strain.

[0918] 10. Cardiac Pacemaker

[0919] In one aspect, the present invention provides a medical device, comprising a cardiac pacemaker (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the medical device and the host into which the medical device is implanted.

[0920] In certain embodiments, the cardiac pacemaker is an adaptive rate pacemaker. In certain other embodiments, the cardiac pacemaker is a rate responsive pacemaker.

[0921] 11. Implantable Cardioverter Defibrillator

[0922] In one aspect, the present invention provides a medical device, comprising an implantable cardioverter defibrillator (ICD) system (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the medical device and the host into which the medical device is implanted.

[0923] Such a medical device may be further defined by one, two, or more of the following features: the implantable cardioverter defibrillator is adapted for treating tachyarraythmias; the implantable cardioverter defibrillator is adapted for ventricular tachycardia; the implantable cardioverter defibrillator is adapted for treating ventricular fibrillation; the implantable cardioverter defibrillator is adapted for treating atrial tachycardia; the implantable cardioverter defibrillator is adapted for treating atrial fibrillation; the implantable cardioverter defibrillator is adapted for treating arrhythmias.

[0924] 12. Implantable Cardioverter Defibrillator

[0925] In one aspect, the present invention provides a medical device, comprising an implantable cardioverter defibrillator (ICD) system (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the medical device and the host into which the medical device is implanted.

[0926] Such a medical device may be further defined by one, two, or more of the following features: the implantable cardioverter defibrillator is adapted for treating tachyarraythmias; the implantable cardioverter defibrillator is adapted for ventricular tachycardia; the implantable cardioverter defibrillator is adapted for treating ventricular fibrillation; the implantable cardioverter defibrillator is adapted for treating atrial tachycardia; the implantable cardioverter defibrillator is adapted for treating atrial fibrillation; and the implantable cardioverter defibrillator is adapted for treating arrhythmias.

[0927] 13. Vagus Nerve Stimulator for Treating Arrhythemia

[0928] In one aspect, the present invention provides a medical device, comprising a vagus nerve stimulator for treating arrhythemia (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the medical device and the host into which the medical device is implanted.

[0929] Such a medical device may be further defined by one, two or more of the following features: the vagus nerve stimulator is adapted for treating supraventricular arrhythmias; the vagus nerve stimulator is adapted for treating angina pectoris; the vagus nerve stimulator is adapted for treating atrial tachycardia; the vagus nerve stimulator is adapted for treating atrial flutter; the vagus nerve stimulator is adapted for treating arterial fibrillation; the vagus nerve stimulator is arrhythmias that result in low cardiac output; and the vagus nerve stimulator comprises a programmable pulse generator.

[0930] 14. Electrical Lead

[0931] In one aspect, the present invention provides a medical device, comprising an electrical lead (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the medical device and the host into which the medical device is implanted.

[0932] Such a medical device may be further defined by one, two or more of the following features: the electrical lead comprises a connector assembly, a conductor and an electrode; the electrical lead is unipolar; the electrical lead is bipolar; the electrical lead is tripolar; the electrical lead is quadripolar; the electrical lead comprises an insulating sheath; the electrical lead is a medical lead; the electrical lead is a cardiac lead; the electrical lead is a pacer lead; the electrical lead is a pacing lead; the electrical lead is a pacemaker lead; the electrical lead is an endocardial lead; the electrical lead is an endocardial pacing lead; the electrical lead is a cardioversion lead; the electrical lead is an epicardial lead; the electrical lead is an epicardial defibrillator lead; the electrical lead is a patch defibrillator; the electrical lead is a patch lead; the electrical lead is an electrical patch; the electrical lead is a transvenous lead; the electrical lead is an active fixation lead; the electrical lead is a passive fixation lead; the electrical lead is a sensing lead; the electrical lead is expandable; the electrical lead has a coil configuration; and the electrical lead has an active fixation element for attachment to host tissue.

[0933] 15. Neurostimulator

[0934] In one aspect, the present invention provides a medical device, comprising a neurostimulator (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the medical device and the host into which the medical device is implanted.

[0935] Such a medical device may be further defined by one, two or more of the following features: the electrical device is a neurostimulator; the electrical device is a spinal cord stimulator; the electrical device is a brain stimulator; the electrical device is a vagus nerve stimulator; the electrical device is a sacral nerve stimulator; the electrical device is a gastric nerve stimulator; the electrical device is an auditory nerve stimulator; the electrical device delivers stimulation to organs; the electrical device delivers stimulation to bone; the electrical device delivers stimulation to muscles; the electrical device delivers stimulation to tissues; the electrical device is a device for continuous subarachnoid infusion; the electrical device is an implantable electrode; the electrical device is an electrical lead; the electrical device is a simulation catheter lead; the electrical device is cochlear implant; the electrical device is a microstimulator; the electrical device is battery powered; the electrical device is radio frequency powered; the electrical device is both battery and radio frequency powered; the electrical device is adapted for treating or preventing pain; the electrical device is adapted for treating or preventing epilepsy; the electrical device is adapted for treating or preventing Parkinson's disease; the electrical device is adapted for treating or preventing movement disorders; the electrical device is adapted for treating or preventing obesity; the electrical device is adapted for treating or preventing depression; the electrical device is adapted for treating or preventing anxiety; the electrical device is adapted for treating or preventing hearing loss; the electrical device is adapted for treating or preventing ulcers; the electrical device is adapted for treating or preventing deep vein thrombosis; the electrical device is adapted for treating or preventing muscular atrophy; the electrical device is adapted for treating or preventing joint stiffness; the electrical device is adapted for treating or preventing muscle spasms; the electrical device is adapted for treating or preventing osteoporosis; the electrical device is adapted for treating or preventing scoliosis; the electrical device is adapted for treating or preventing spinal disc degeneration; the electrical device is adapted for treating or preventing spinal cord injury; the electrical device is adapted for treating or preventing urinary dysfunction; the electrical device is adapted for treating or preventing gastroparesis; the electrical device is adapted for treating or preventing malignancy; the electrical device is adapted for treating or preventing arachnoiditis; the electrical device is adapted for treating or preventing chronic disease; the electrical device is adapted for treating or preventing migraine; the electrical device is adapted for treating or preventing sleep disorders; the electrical device is adapted for treating or preventing dementia; and the electrical device is adapted for treating or preventing Alzheimer's disease.

[0936] 16. Cardiac Rhythm Management Device

[0937] In one aspect, the present invention provides a medical device, comprising a cardiac rhythm management device (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the medical device and the host into which the medical device is implanted.

[0938] Such a medical device may be defined by one, two or more of the following features: the electrical device is an implantable pulse generator; the electrical device is an electrical lead; the electrical device is a stimulation lead; the electrical device is a simulation catheter lead; the electrical device is a microstimulator; the electrical device is battery powered; the electrical device is radio frequency powered; the electrical device is both battery and radio frequency powered; the electrical device is a cardiac pacemaker; the electrical device is an implantable cardioverter defibrillator system; the electrical device is a cardiac lead; the electrical device is a pacer lead; the electrical device is an endocardial lead; the electrical device is a cardioversion/defibrillator lead; the electrical device is an epicardial lead; the electrical device is an epicardial defibrillator lead; the electrical device is a patch defibrillator; the electrical device is a patch defibrillator lead; the electrical device is an electrical patch; the electrical device is a transvenous lead; the electrical device is an active fixation lead; the electrical device is a passive fixation lead; the electrical device is a sensing lead; the electrical device is a defibrillator; the electrical device is an implantable sensor; the electrical device is a left ventricular assist device; the electrical device is a pulse generator; the electrical device is a patch lead; the electrical device is an electrical patch; the electrical device is a cardiac stimulator; the electrical device is an electrical deviceable sensor; the electrical device is an electrical deviceable pump; the electrical device is a dural patch; the electrical device is a ventricular peritoneal shunt; the electrical device is a ventricular atrial shunt; the electrical device is adapted for treating or preventing epidural fibrosis post-laminectomy; the electrical device is adapted for treating or pre-

venting cardiac rhythm abnormalities; the electrical device is adapted for treating or preventing atrial rhythm abnormalities; the electrical device is adapted for treating or preventing conduction abnormalities; and the electrical device is adapted for treating or preventing ventricular rhythm abnormalities.

[0939] Additional Features Related to Medical Devices

[0940] The medical devices described above may also be defined by one, two or more of the following features: the agent inhibits cell regeneration; the agent inhibits angiogenesis; the agent inhibits fibroblast migration; the agent inhibits fibroblast proliferation; the agent inhibits deposition of extracellular matrix; the agent inhibits tissue remodeling; the agent is an angiogenesis inhibitor; the agent is a 5-lipoxygenase inhibitor or antagonist; the agent is a chemokine receptor antagonist; the agent is a cell cycle inhibitor; the agent is a taxane; the agent is an anti-microtubule agent; the agent is paclitaxel; the agent is not paclitaxel; the agent is an analogue or derivative of paclitaxel, the agent is a vinca alkaloid; the agent is camptothecin or an analogue or derivative thereof; the agent is a podophyllotoxin; the agent is a podophyllotoxin, wherein the podophyllotoxin is etoposide or an analogue or derivative thereof; the agent is an anthracycline; the agent is an anthracycline, wherein the anthracycline is doxorubicin or an analogue or derivative thereof; the agent is an anthracycline, wherein the anthracycline is mitoxantrone or an analogue or derivative thereof; the agent is a platinum compound; the agent is a nitrosourea; the agent is a nitroimidazole; the agent is a folic acid antagonist; the agent is a cytidine analogue; the agent is a pyrimidine analogue; the agent is a fluoropyrimidine analogue; the agent is a purine analogue; the agent is a nitrogen mustard or an analogue or derivative thereof; the agent is a hydroxyurea; the agent is a mytomicin or an analogue or derivative thereof; the agent is an alkyl sulfonate; the agent is a benzamide or an analogue or derivative thereof; the agent is a nicotinamide or an analogue or derivative thereof; the agent is a halogenated sugar or an analogue or derivative thereof; the agent is a DNA alkylating agent; the agent is an anti-microtubule agent; the agent is a topoisomerase inhibitor; the agent is a DNA cleaving agent; the agent is an antimetabolite; the agent inhibits adenosine deaminase; the agent inhibits purine ring synthesis; the agent is a nucleotide interconversion inhibitor; the agent inhibits dihydrofolate reduction; the agent blocks thymidine monophosphate; the agent causes DNA damage; the agent is a DNA intercalation agent; the agent is a RNA synthesis inhibitor; the agent is a pyrimidine synthesis inhibitor; the agent inhibits ribonucleotide synthesis or function; the agent inhibits thymidine monophosphate synthesis or function; the agent inhibits DNA synthesis; the agent causes DNA adduct formation; the agent inhibits protein synthesis; the agent inhibits microtubule function; the agent is a cyclin dependent protein kinase inhibitor; the agent is an epidermal growth factor kinase inhibitor; the agent is an elastase inhibitor; the agent is a factor Xa inhibitor; the agent is a farnesyltransferase inhibitor; the agent is a fibrinogen antagonist; the agent is a guanylate cyclase stimulant; the agent is a heat shock protein 90 antagonist; the agent is a heat shock protein 90 antagonist, wherein the heat shock protein 90 antagonist is geldanamycin or an analogue or derivative thereof; the agent is a guanylate cyclase stimulant; the agent is a HMGCoA reductase inhibitor; the agent is a HMGCoA reductase inhibitor, wherein the HMGCoA reductase inhibitor is simvastatin or an analogue or derivative thereof; the agent is a hydroorotate dehydrogenase inhibitor; the agent is an IKK2 inhibitor; the agent is an IL-1 antagonist; the agent is an ICE antagonist; the agent is an IRAK antagonist; the agent is an IL-4 agonist; the agent is an immunomodulatory agent; the agent is sirolimus or an analogue or derivative thereof; the agent is not sirolimus; the agent is everolimus or an analogue or derivative thereof; the agent is tacrolimus or an analogue or derivative thereof; the agent is not tacrolimus; the agent is biolmus or an analogue or derivative thereof; the agent is tresperimus or an analogue or derivative thereof; the agent is auranofin or an analogue or derivative thereof; the agent is 27-0-demethylrapamycin or an analogue or derivative thereof; the agent is gusperimus or an analogue or derivative thereof; the agent is pimecrolimus or an analogue or derivative thereof; the agent is ABT-578 or an analogue or derivative thereof; the agent is an inosine monophosphate dehydrogenase (IMPDH) inhibitor; the agent is an IMPDH inhibitor, wherein the IMPDH inhibitor is mycophenolic acid or an analogue or derivative thereof; the agent is an IMPDH inhibitor, wherein the IMPDH inhibitor is 1-alpha-25 dihydroxy vitamin D_3 or an analogue or derivative thereof; the agent is a leukotriene inhibitor; the agent is a MCP-1 antagonist; the agent is a MMP inhibitor; the agent is an NF kappa B inhibitor; the agent is an NF kappa B inhibitor, wherein the NF kappa B inhibitor is Bay 11-7082; the agent is an NO antagonist; the agent is a p38 MAP kinase inhibitor; the agent is a p38 MAP kinase inhibitor, wherein the p38 MAP kinase inhibitor is SB 202190; the agent is a phosphodiesterase inhibitor; the agent is a TGF beta inhibitor; the agent is a thromboxane A2 antagonist; the agent is a TNFα antagonist; the agent is a TACE inhibitor; the agent is a tyrosine kinase inhibitor; the agent is a vitronectin inhibitor; the agent is a fibroblast growth factor inhibitor; the agent is a protein kinase inhibitor; the agent is a PDGF receptor kinase inhibitor; the agent is an endothelial growth factor receptor kinase inhibitor; the agent is a retinoic acid receptor antagonist; the agent is a platelet derived growth factor receptor kinase inhibitor; the agent is a fibrinogen antagonist; the agent is an antimycotic agent; the agent is an antimycotic agent, wherein the antimycotic agent is sulconizole; the agent is a bisphosphonate; the agent is a phospholipase A1 inhibitor; the agent is a histamine H1/H2/H3 receptor antagonist; the agent is a macrolide antibiotic; the agent is a GPIIb/IIIa receptor antagonist; the agent is an endothelin receptor antagonist; the agent is a peroxisome proliferator-activated receptor agonist; the agent is an estrogen receptor agent; the agent is a somastostatin analogue; the agent is a neurokinin 1 antagonist; the agent is a neurokinin 3 antagonist; the agent is a VLA-4 antagonist; the agent is an osteoclast inhibitor; the agent is a DNA topoisomerase ATP hydrolyzing inhibitor; the agent is an angiotensin I converting enzyme inhibitor; the agent is an angiotensin II antagonist; the agent is an enkephalinase inhibitor; the agent is a peroxisome proliferator-activated receptor gamma agonist insulin sensitizer; the agent is a protein kinase C inhibitor; the agent is a ROCK (rho-associated kinase) inhibitor; the agent is a CXCR3 inhibitor; the agent is an ltk inhibitor; the agent is a cytosolic phospholipase A_2-alpha inhibitor; the agent is a PPAR agonist; the agent is an immunosuppressant; the agent is an Erb inhibitor; the agent is an apoptosis agonist; the agent is a lipocortin agonist; the agent is a VCAM-1 antagonist; the agent is a collagen antagonist; the agent is an alpha 2 integrin antago-

nist; the agent is a TNF alpha inhibitor; the agent is a nitric oxide inhibitor; the agent is a cathepsin inhibitor; the agent is not an anti-inflammatory agent; the agent is not a steroid; the agent is not a glucocorticosteroid; the agent is not dexamethasone, beclomethasone, or dipropionate; the agent is not an anti-infective agent; the agent is not an antibiotic; the agent is not an anti-fugal agent; the agent is not beclomethasone; the agent is not dipropionate; the medical device further comprises a coating, wherein the coating comprises the anti-scarring agent and a polymer; the medical device further comprises a coating, wherein the coating comprises the anti-scarring agent; the medical device further comprises a coating, wherein the coating is disposed on a surface of the electrical device; the medical device further comprises a coating, wherein the coating directly contacts the electrical device; the medical device further comprises a coating, wherein the coating indirectly contacts the electrical device; the medical device further comprises a coating, wherein the coating partially covers the electrical device; the medical device further comprises a coating, wherein the coating completely covers the electrical device; the medical device further comprises a coating, wherein the coating is a uniform coating; the medical device further comprises a coating, wherein the coating is a non-uniform coating; the medical device further comprises a coating, wherein the coating is a discontinuous coating; the medical device further comprises a coating, wherein the coating is a patterned coating; the medical device further comprises a coating, wherein the coating has a thickness of 100 μm or less; the medical device further comprises a coating, wherein the coating has a thickness of 10 μm or less; the medical device further comprises a coating, wherein the coating adheres to the surface of the electrical device upon deployment of the medical device; the medical device further comprises a coating, wherein the coating is stable at room temperature for a period of 1 year; the medical device further comprises a coating, wherein the anti-scarring agent is present in the coating in an amount ranging between about 0.0001% to about 1% by weight; the medical device further comprises a coating, wherein the anti-scarring agent is present in the coating in an amount ranging between about 1% to about 10% by weight; the medical device further comprises a coating, wherein the anti-scarring agent is present in the coating in an amount ranging between about 10% to about 25% by weight; the medical device further comprises a coating, wherein the anti-scarring agent is present in the coating in an amount ranging between about 25% to about 70% by weight; the medical device further comprises a coating, wherein the coating further comprises a polymer; the medical device further comprises a first coating having a first composition and the second coating having a second composition; the medical device further comprises a first coating having a first composition and the second coating having a second composition, wherein the first composition and the second composition are different; the medical device further comprises a polymer; the medical device further comprises a polymeric carrier; the medical device further comprises a polymeric carrier, wherein the polymeric carrier comprises a copolymer; the medical device further comprises a polymeric carrier, wherein the polymeric carrier comprises a block copolymer; the medical device further comprises a polymeric carrier, wherein the polymeric carrier comprises a random copolymer; the medical device further comprises a polymeric carrier, wherein the polymeric carrier comprises a biodegradable polymer; the medical device further comprises a polymeric carrier, wherein the polymeric carrier comprises a non-biodegradable polymer; the medical device further comprises a polymeric carrier, wherein the polymeric carrier comprises a hydrophilic polymer; the medical device further comprises a polymeric carrier, wherein the polymeric carrier comprises a hydrophobic polymer; the medical device further comprises a polymeric carrier, wherein the polymeric carrier comprises a polymer having hydrophilic domains; the medical device further comprises a polymeric carrier, wherein the polymeric carrier comprises a polymer having hydrophobic domains; the medical device further comprises a polymeric carrier, wherein the polymeric carrier comprises a non-conductive polymer; the medical device further comprises a polymeric carrier, wherein the polymeric carrier comprises an elastomer; the medical device further comprises a polymeric carrier, wherein the polymeric carrier comprises a hydrogel; the medical device further comprises a polymeric carrier, wherein the polymeric carrier comprises a silicone polymer; the medical device further comprises a polymeric carrier, wherein the polymeric carrier comprises a hydrocarbon polymer; the medical device further comprises a polymeric carrier, wherein the polymeric carrier comprises a styrene-derived polymer; the medical device further comprises a polymeric carrier, wherein the polymeric carrier comprises a butadiene polymer; the medical device further comprises a polymeric carrier, wherein the polymeric carrier comprises a macromer; the medical device further comprises a polymeric carrier, wherein the polymeric carrier comprises a poly(ethylene glycol) polymer; the medical device further comprises a polymeric carrier, wherein the polymeric carrier comprises an amorphous polymer; the medical device further comprises a lubricious coating; the anti-scarring agent is located within pores or holes of the electrical device; the anti-scarring agent is located within a channel, lumen, or divet of the electrical device; the medical device further comprises a second pharmaceutically active agent; the medical device further comprises an anti-inflammatory agent; the medical device further comprises an agent that inhibits infection; the medical device further comprises an agent that inhibits infection, wherein the agent is an anthracycline; the medical device further comprises an agent that inhibits infection, wherein the agent is doxorubicin; the medical device further comprises an agent that inhibits infection, wherein the agent is mitoxantrone; the medical device further comprises an agent that inhibits infection, wherein the agent is a fluoropyrimidine; the medical device further comprises an agent that inhibits infection, wherein the agent is 5-fluorouracil (5-FU); the medical device further comprises an agent that inhibits infection, wherein the agent is a folic acid antagonist; the medical device further comprises an agent that inhibits infection, wherein the agent is methotrexate; the medical device further comprises an agent that inhibits infection, wherein the agent is a podophylotoxin; the medical device further comprises an agent that inhibits infection, wherein the agent is etoposide; the medical device further comprises an agent that inhibits infection, wherein the agent is a camptothecin; the medical device further comprises an agent that inhibits infection, wherein the agent is a hydroxyurea; the medical device further comprises an agent that inhibits infection, wherein the agent is a platinum complex; the medical device further comprises an agent that inhibits infection, wherein the agent is cisplatin; the medical

device further comprises an anti-thrombotic agent; the medical device further comprises a visualization agent; the medical device further comprises a visualization agent, wherein the visualization agent is a radiopaque material, wherein the radiopaque material comprises a metal, a halogenated compound, or a barium containing compound; the medical device further comprises a visualization agent, wherein the visualization agent is a radiopaque material, wherein the radiopaque material comprises barium, tantalum, or technetium; the medical device further comprises a visualization agent, wherein the visualization agent is a MRI responsive material; the medical device further comprises a visualization agent, wherein the visualization agent comprises a gadolinium chelate; the medical device further comprises a visualization agent, wherein the visualization agent comprises iron, magnesium, manganese, copper, or chromium; the medical device further comprises a visualization agent, wherein the visualization agent comprises an iron oxide compound; the medical device further comprises a visualization agent, wherein the visualization agent comprises a dye, pigment, or colorant; the medical device further comprises an echogenic material; the medical device further comprises an echogenic material, wherein the echogenic material is in the form of a coating; the device is sterile; the anti-scarring agent inhibits adhesion between the medical device and a host into which the medical device is implanted; the medical device delivers the anti-scarring agent locally to tissue proximate to the medical device; the anti-scarring agent is released into tissue in the vicinity of the medical device after deployment of the medical device; the anti-scarring agent is released into tissue in the vicinity of the medical device after deployment of the medical device, wherein the tissue is connective tissue; the anti-scarring agent is released into tissue in the vicinity of the medical device after deployment of the medical device, wherein the tissue is muscle tissue; the anti-scarring agent is released into tissue in the vicinity of the medical device after deployment of the medical device, wherein the tissue is nerve tissue; the anti-scarring agent is released into tissue in the vicinity of the medical device after deployment of the medical device, wherein the tissue is epithelium tissue; the anti-scarring agent is released in effective concentrations from the medical device over a period ranging from the time of deployment of the medical device to about 1 year; the anti-scarring agent is released in effective concentrations from the medical device over a period ranging from about 1 month to 6 months; the anti-scarring agent is released in effective concentrations from the medical device over a period ranging from about 1-90 days; the anti-scarring agent is released in effective concentrations from the medical device at a constant rate; the anti-scarring agent is released in effective concentrations from the medical device at an increasing rate; the anti-scarring agent is released in effective concentrations from the medical device at a decreasing rate; the anti-scarring agent is released in effective concentrations from the composition comprising the anti-scarring agent by diffusion over a period ranging from the time of deployment of the medical device to about 90 days; the anti-scarring agent is released in effective concentrations from the composition comprising the anti-scarring agent by erosion of the composition over a period ranging from the time of deployment of the medical device to about 90 days; the device comprises about 0.01 μg to about 10 μg of the anti-scarring agent; the device comprises about 10 μg to about 10 mg of the anti-scarring agent; the device comprises about 10 mg to about 250 mg of the anti-scarring agent; the device comprises about 250 mg to about 1000 mg of the anti-scarring agent; the device comprises about 1000 mg to about 2500 mg of the anti-scarring agent; a surface of the device comprises less than 0.01 μg of the anti-scarring agent per mm^2 of device surface to which the anti-scarring agent is applied; a surface of the device comprises about 0.01 μg to about 1 μg of the anti-scarring agent per mm^2 of device surface to which the anti-scarring agent is applied; a surface of the device comprises about 1 μg to about 10 μg of the anti-scarring agent per mm^2 of device surface to which the anti-scarring agent is applied; a surface of the device comprises about 10 μg to about 250 μg of the anti-scarring agent per mm^2 of device surface to which the anti-scarring agent is applied; a surface of the device comprises about 250 μg to about 1000 μg of the anti-scarring agent of anti-scarring agent per mm^2 of device surface to which the anti-scarring agent is applied; a surface of the device comprises about 1000 μg to about 2500 μg of the anti-scarring agent per mm^2 of device surface to which the anti-scarring agent is applied; the agent or the composition is affixed to the electrical device; the agent or the composition is covalently attached to the electrical device; the agent or the composition is non-covalently attached to the electrical device; the medical device further comprises a coating that absorbs the agent or the composition; the electrical device is interweaved with a thread composed of, or coated with, the agent or the composition; a portion of the electrical device is covered with a sleeve that contains the agent or the composition; the electrical device is completely covered with a sleeve that contains the agent or the composition; a portion of the electrical device is covered with a mesh that contains the agent or the composition; and the electrical device is completely covered with a mesh that contains the agent or the composition.

[0941] The present invention, in various aspects and embodiments, provides the following methods for inhibiting scarring:

[0942] 1. Electrical Device

[0943] In one aspect, the present invention provides a method for inhibiting scarring comprising placing an electrical device and an anti-scarring agent or a composition comprising an ant-scarring agent into an animal host, wherein the agent inhibits scarring.

[0944] Such a method may be defined by one, two, or more of the following features: the electrical device is a neurostimulator; the electrical device is a spinal cord stimulator; the electrical device is a brain stimulator; the electrical device is a vagus nerve stimulator; the electrical device is a sacral nerve stimulator; the electrical device is a gastric nerve stimulator; the electrical device is an auditory nerve stimulator; the electrical device delivers stimulation to organs; the electrical device delivers stimulation to bone; the electrical device delivers stimulation to muscles; the electrical device delivers stimulation to tissues; the electrical device is a device for continuous subarachnoid infusion; the electrical device is an implantable electrode; the electrical device is an implantable pulse generator, the electrical device is an electrical lead; the electrical device is a stimulation lead; the electrical device is a simulation catheter lead; the electrical device is cochlear implant; the electrical device

is a microstimulator; the electrical device is battery powered; the electrical device is radio frequency powered; the electrical device is both battery and radio frequency powered; the electrical device is a cardiac rhythm management device; the electrical device is a cardiac pacemaker; the electrical device is an implantable cardioverter defibrillator system; the electrical device is a cardiac lead; the electrical device is a pacer lead; the electrical device is an endocardial lead; the electrical device is a cardioversion/defibrillator lead; the electrical device is an epicardial lead; the electrical device is an epicardial defibrillator lead; the electrical device is a patch defibrillator; the electrical device is a patch defibrillator lead; the electrical device is an electrical patch; the electrical device is a transvenous lead; the electrical device is an active fixation lead; the electrical device is a passive fixation lead; the electrical device is a sensing lead; the electrical device is a defibrillator; the electrical device is an implantable sensor; the electrical device is a left ventricular assist device; the electrical device is a pulse generator; the electrical device is a patch lead; the electrical device is an electrical patch; the electrical device is a cardiac stimulator; the electrical device is an electrical deviceable sensor; the electrical device is an electrical deviceable pump; the electrical device is a dural patch; the electrical device is a ventricular peritoneal shunt; the electrical device is a ventricular atrial shunt; the electrical device is adapted for treating or preventing epidural fibrosis post-laminectomy; the electrical device is adapted for treating or preventing cardiac rhythm abnormalities; the electrical device is adapted for treating or preventing atrial rhythm abnormalities; the electrical device is adapted for treating or preventing conduction abnormalities; the electrical device is adapted for treating or preventing ventricular rhythm abnormalities; the electrical device is adapted for treating or preventing pain; the electrical device is adapted for treating or preventing epilepsy; the electrical device is adapted for treating or preventing Parkinson's disease; the electrical device is adapted for treating or preventing movement disorders; the electrical device is adapted for treating or preventing obesity; the electrical device is adapted for treating or preventing depression; the electrical device is adapted for treating or preventing anxiety; the electrical device is adapted for treating or preventing hearing loss; the electrical device is adapted for treating or preventing ulcers; the electrical device is adapted for treating or preventing deep vein thrombosis; the electrical device is adapted for treating or preventing muscular atrophy; the electrical device is adapted for treating or preventing joint stiffness; the electrical device is adapted for treating or preventing muscle spasms; the electrical device is adapted for treating or preventing osteoporosis; the electrical device is adapted for treating or preventing scoliosis; the electrical device is adapted for treating or preventing spinal disc degeneration; the electrical device is adapted for treating or preventing spinal cord injury; the electrical device is adapted for treating or preventing urinary dysfunction; the electrical device is adapted for treating or preventing gastroparesis; the electrical device is adapted for treating or preventing malignancy; the electrical device is adapted for treating or preventing arachnoiditis; the electrical device is adapted for treating or preventing chronic disease; the electrical device is adapted for treating or preventing migraine; the electrical device is adapted for treating or preventing sleep disorders; the electrical device is adapted for treating or preventing dementia; and the electrical device is adapted for treating or preventing Alzheimer's disease.

[0945] 2. Neurostimulator for Treating Chronic Pain

[0946] In one aspect, the present invention provides a method for inhibiting scarring comprising placing a neurostimulator for treating chronic pain (i.e., an electrical device) and an anti-scarring agent or a composition comprising an ant-scarring agent into an animal host, wherein the agent inhibits scarring.

[0947] Such a method may be further defined by one, two, or more of the following features: the chronic pain results from injury; the chronic pain results from an illness; the chronic pain results from scoliosis; the chronic pain results from spinal disc degeneration; the chronic pain results from malignancy; the chronic pain results from arachnoiditis; the chronic pain results from a chronic disease; the chronic pain results from a pain syndrome; the neurostimulator comprises a lead that delivers electrical stimulation to a nerve and an electrical connection that connects a power source to the lead; the neurostimulator is adapted for spinal cord stimulation, and comprises a sensor that detects the position of the spine and a stimulator that emits pulses that decrease in amplitude when the back is in a supine position; the neurostimulator comprises an electrode and a control circuit that generates pulses and rest period based on intervals corresponding to the host body's activity and regeneration period; the neurostimulator comprises a stimulation catheter lead and an electrode; and the neurostimulator is a self-centering epidural spinal cord lead.

[0948] 3. Neurostimulator for Treating Parkinson's Disease

[0949] In one aspect, the present invention provides a method for inhibiting scarring comprising placing a neurostimulator for treating Parkinson's Disease (i.e., an electrical device) and an anti-scarring agent or a composition comprising an ant-scarring agent into an animal host, wherein the agent inhibits scarring.

[0950] In certain embodiments, the neurostimulator comprises an intracranially implantable electrical control module and an electrode. In other embodiments, the neurostimulator comprises a sensor and an electrode.

[0951] 4. Vagal Nerve Stimulator for Treating Epilepsy

[0952] In one aspect, the present invention provides a method for inhibiting scarring comprising placing a vagal nerve stimulator for treating epilepsy (i.e., an electrical device) and an anti-scarring agent or a composition comprising an ant-scarring agent into an animal host, wherein the agent inhibits scarring.

[0953] 5. Vagal Nerve Stimulator for Treating Other Disorders

[0954] In one aspect, the present invention provides a method for inhibiting scarring comprising placing a vagal nerve stimulator (i.e., an electrical device) and an anti-scarring agent or a composition comprising an ant-scarring agent into an animal host, wherein the agent inhibits scarring.

[0955] Such a method may be further defined by one, two or more of the following features: the vagal nerve stimulator is adapted for treating or preventing depression; the vagal

nerve stimulator is adapted for treating or preventing anxiety; the vagal nerve stimulator is adapted for treating or preventing panic disorders; the vagal nerve stimulator is adapted for treating or preventing obsessive-compulsive disorders; the vagal nerve stimulator is adapted for treating or preventing post-traumatic disorders; the vagal nerve stimulator is adapted for treating or preventing obesity; the vagal nerve stimulator is adapted for treating or preventing migraine; the vagal nerve stimulator is adapted for treating or preventing sleep disorders; the vagal nerve stimulator is adapted for treating or preventing dementia; the vagal nerve stimulator is adapted for treating or preventing Alzheimer's disease; and the vagal nerve stimulator is adapted for treating or preventing chronic or degenerative neurological disorders.

[0956] 6. Sacral Nerve Stimulator

[0957] In one aspect, the present invention provides a method for inhibiting scarring comprising placing a sacral nerve stimulator for treating a bladder control problem (i.e., an electrical device) and an anti-scarring agent or a composition comprising an ant-scarring agent into an animal host, wherein the agent inhibits scarring.

[0958] Such a method may be further defined by one, two, or more of the following features: the sacral nerve stimulator is adapted for treating or preventing urge incontinence; the sacral nerve stimulator is adapted for treating or preventing nonobstructive urinary retention; the sacral nerve stimulator is adapted for treating or preventing urgency frequency; the sacral nerve stimulator is an intramuscular electrical stimulator; and the sacral nerve stimulator is a leadless, tubular-shaped microstimulator.

[0959] 7. Gastric Nerve Stimulator

[0960] In one aspect, the present invention provides a method for inhibiting scarring comprising placing a gastric nerve stimulator for treating a gastrointestinal disorder (i.e., an electrical device) and an anti-scarring agent or a composition comprising an ant-scarring agent into an animal host, wherein the agent inhibits scarring.

[0961] Such a method may be further defined by one, two, or more of the following features: the gastric nerve stimulator is adapted for treating or preventing morbid obesity; the gastric nerve stimulator is adapted for treating or preventing constipation; the gastric nerve stimulator comprises an electrical lead, an electrode and a stimulation generator; and the gastric nerve stimulator comprises an electrical signal controller, connector wire and an attachment lead.

[0962] 8. Cochlear Implant

[0963] The present invention provides a method for inhibiting scarring comprising placing a cochlear implant for treating deafness (i.e., an electrical device) and an anti-scarring agent or a composition comprising an ant-scarring agent into an animal host, wherein the agent inhibits scarring.

[0964] Such a method may be further defined by one, two or more the following features: the cochlear implant comprises a plurality of transducer elements; the cochlear implant comprises a sound-to-electrical stimulation encoder, a body implantable receiver-stimulator, and electrodes; the cochlear implant comprises a transducer and an electrode array; and the cochlear implant is a subcranially implantable electomechanical system.

[0965] 9. Bone Growth Stimulator

[0966] In one aspect, the present invention provides a method for inhibiting scarring comprising placing a bone growth stimulator (i.e., an electrical device) and an anti-scarring agent or a composition comprising an ant-scarring agent into an animal host, wherein the agent inhibits scarring.

[0967] In certain embodiments, the bone growth stimulator comprises an electrode and a generator having a strain response piezoelectric material that responds to strain.

[0968] 10. Cardiac Pacemaker

[0969] In one aspect, the present invention provides a method for inhibiting scarring comprising placing a cardiac pacemaker (i.e., an electrical device) and an anti-scarring agent or a composition comprising an ant-scarring agent into an animal host, wherein the agent inhibits scarring.

[0970] In certain embodiments, the cardiac pacemaker is an adaptive rate pacemaker. In certain other embodiments, the cardiac pacemaker is a rate responsive pacemaker.

[0971] 11. Implantable Cardioverter Defibrillator

[0972] In one aspect, the present invention provides a method for inhibiting scarring comprising placing an implantable cardioverter defibrillator (ICD) system (i.e., an electrical device) and an anti-scarring agent or a composition comprising an ant-scarring agent into an animal host, wherein the agent inhibits scarring.

[0973] Such a method may be further defined by one, two, or more of the following features: the implantable cardioverter defibrillator is adapted for treating tachyarraythmias; the implantable cardioverter defibrillator is adapted for ventricular tachycardia; the implantable cardioverter defibrillator is adapted for treating ventricular fibrillation; the implantable cardioverter defibrillator is adapted for treating atrial tachycardia; the implantable cardioverter defibrillator is adapted for treating atrial fibrillation; the implantable cardioverter defibrillator is adapted for treating arrhythmias.

[0974] 12. Vagus Nerve Stimulator for Treating Arrhythemia

[0975] In one aspect, the present invention provides a method for inhibiting scarring comprising placing a vagus nerve stimulator for treating arrhythemia (i.e., an electrical device) and an anti-scarring agent or a composition comprising an ant-scarring agent into an animal host, wherein the agent inhibits scarring.

[0976] Such a method may be further defined by one, two or more of the following features: the vagus nerve stimulator is adapted for treating supraventricular arrhythmias; the vagus nerve stimulator is adapted for treating angina pectoris; the vagus nerve stimulator is adapted for treating atrial tachycardia; the vagus nerve stimulator is adapted for treating atrial flutter; the vagus nerve stimulator is adapted for treating arterial fibrillation; the vagus nerve stimulator is arrhythmias that result in low cardiac output; and the vagus nerve stimulator comprises a programmable pulse generator.

[0977] 13. Electrical Lead

[0978] In one aspect, the present invention provides a method for inhibiting scarring comprising placing an elec-

trical lead (i.e., an electrical device) and an anti-scarring agent or a composition comprising an ant-scarring agent into an animal host, wherein the agent inhibits scarring.

[0979] Such a method may be further defined by one, two or more of the following features: the electrical lead comprises a connector assembly, a conductor and an electrode; the electrical lead is unipolar; the electrical lead is bipolar; the electrical lead is tripolar; the electrical lead is quadripolar; the electrical lead comprises an insulating sheath; the electrical lead is a medical lead; the electrical lead is a cardiac lead; the electrical lead is a pacer lead; the electrical lead is a pacing lead; the electrical lead is a pacemaker lead; the electrical lead is an endocardial lead; the electrical lead is an endocardial pacing lead; the electrical lead is a cardioversion lead; the electrical lead is an epicardial lead; the electrical lead is an epicardial defibrillator lead; the electrical lead is a patch defibrillator; the electrical lead is a patch lead; the electrical lead is an electrical patch; the electrical lead is a transvenous lead; the electrical lead is an active fixation lead; the electrical lead is a passive fixation lead; the electrical lead is a sensing lead; the electrical lead is expandable; the electrical lead has a coil configuration; and the electrical lead has an active fixation element for attachment to host tissue.

[0980] 14. Neurostimulator

[0981] In one aspect, the present invention provides a method for inhibiting scarring comprising placing a neurostimulator (i.e., an electrical device) and an anti-scarring agent or a composition comprising an ant-scarring agent into an animal host, wherein the agent inhibits scarring.

[0982] Such a method may be further defined by one, two or more of the following features: the electrical device is a neurostimulator; the electrical device is a spinal cord stimulator; the electrical device is a brain stimulator; the electrical device is a vagus nerve stimulator; the electrical device is a sacral nerve stimulator; the electrical device is a gastric nerve stimulator; the electrical device is an auditory nerve stimulator; the electrical device delivers stimulation to organs; the electrical device delivers stimulation to bone; the electrical device delivers stimulation to muscles; the electrical device delivers stimulation to tissues; the electrical device is a device for continuous subarachnoid infusion; the electrical device is an implantable electrode; the electrical device is an electrical lead; the electrical device is a simulation catheter lead; the electrical device is cochlear implant; the electrical device is a microstimulator; the electrical device is battery powered; the electrical device is radio frequency powered; the electrical device is both battery and radio frequency powered; the electrical device is adapted for treating or preventing pain; the electrical device is adapted for treating or preventing epilepsy; the electrical device is adapted for treating or preventing Parkinson's disease; the electrical device is adapted for treating or preventing movement disorders; the electrical device is adapted for treating or preventing obesity; the electrical device is adapted for treating or preventing depression; the electrical device is adapted for treating or preventing anxiety; the electrical device is adapted for treating or preventing hearing loss; the electrical device is adapted for treating or preventing ulcers; the electrical device is adapted for treating or preventing deep vein thrombosis; the electrical device is adapted for treating or preventing muscular atrophy; the electrical device is adapted for treating or preventing joint stiffness; the electrical device is adapted for treating or preventing muscle spasms; the electrical device is adapted for treating or preventing osteoporosis; the electrical device is adapted for treating or preventing scoliosis; the electrical device is adapted for treating or preventing spinal disc degeneration; the electrical device is adapted for treating or preventing spinal cord injury; the electrical device is adapted for treating or preventing urinary dysfunction; the electrical device is adapted for treating or preventing gastroparesis; the electrical device is adapted for treating or preventing malignancy; the electrical device is adapted for treating or preventing arachnoiditis; the electrical device is adapted for treating or preventing chronic disease; the electrical device is adapted for treating or preventing migraine; the electrical device is adapted for treating or preventing sleep disorders; the electrical device is adapted for treating or preventing dementia; and the electrical device is adapted for treating or preventing Alzheimer's disease.

[0983] 15. Cardiac Rhythm Management Device

[0984] In one aspect, the present invention provides a method for inhibiting scarring comprising placing a cardiac rhythm management device (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent into an animal host, wherein the agent inhibits scarring.

[0985] Such a method may be defined by one, two or more of the following features: the electrical device is an implantable pulse generator; the electrical device is an electrical lead; the electrical device is a stimulation lead; the electrical device is a simulation catheter lead; the electrical device is a microstimulator; the electrical device is battery powered; the electrical device is radio frequency powered; the electrical device is both battery and radio frequency powered; the electrical device is a cardiac pacemaker; the electrical device is an implantable cardioverter defibrillator system; the electrical device is a cardiac lead; the electrical device is a pacer lead; the electrical device is an endocardial lead; the electrical device is a cardioversion/defibrillator lead; the electrical device is an epicardial lead; the electrical device is an epicardial defibrillator lead; the electrical device is a patch defibrillator; the electrical device is a patch defibrillator lead; the electrical device is an electrical patch; the electrical device is a transvenous lead; the electrical device is an active fixation lead; the electrical device is a passive fixation lead; the electrical device is a sensing lead; the electrical device is a defibrillator; the electrical device is an implantable sensor; the electrical device is a left ventricular assist device; the electrical device is a pulse generator; the electrical device is a patch lead; the electrical device is an electrical patch; the electrical device is a cardiac stimulator; the electrical device is an electrical deviceable sensor; the electrical device is an electrical deviceable pump; the electrical device is a dural patch; the electrical device is a ventricular peritoneal shunt; the electrical device is a ventricular atrial shunt; the electrical device is adapted for treating or preventing epidural fibrosis post-laminectomy; the electrical device is adapted for treating or preventing cardiac rhythm abnormalities; the electrical device is adapted for treating or preventing atrial rhythm abnormalities; the electrical device is adapted for treating or prevent-

ing conduction abnormalities; and the electrical device is adapted for treating or preventing ventricular rhythm abnormalities.

[0986] Additional Features Related to Methods for Inhibiting Scarring

[0987] The methods for inhibiting scarring may also be further defined by one, two, or more of the following features: the agent inhibits cell regeneration; the agent inhibits angiogenesis; the agent inhibits fibroblast migration; the agent inhibits fibroblast proliferation; the agent inhibits deposition of extracellular matrix; the agent inhibits tissue remodeling; the agent is an angiogenesis inhibitor; the agent is a 5-lipoxygenase inhibitor or antagonist; the agent is a chemokine receptor antagonist; the agent is a cell cycle inhibitor; the agent is a taxane; the agent is an anti-microtubule agent; the agent is paclitaxel; the agent is not paclitaxel; the agent is an analogue or derivative of paclitaxel; the agent is a vinca alkaloid; the agent is camptothecin or an analogue or derivative thereof; the agent is a podophyllotoxin; the agent is a podophyllotoxin, wherein the podophyllotoxin is etoposide or an analogue or derivative thereof; the agent is an anthracycline; the agent is an anthracycline, wherein the anthracycline is doxorubicin or an analogue or derivative thereof; the agent is an anthracycline, wherein the anthracycline is mitoxantrone or an analogue or derivative thereof; the agent is a platinum compound; the agent is a nitrosourea; the agent is a nitroimidazole; the agent is a folic acid antagonist; the agent is a cytidine analogue; the agent is a pyrimidine analogue; the agent is a fluoropyrimidine analogue; the agent is a purine analogue; the agent is a nitrogen mustard or an analogue or derivative thereof; the agent is a hydroxyurea; the agent is a mytomicin or an analogue or derivative thereof; the agent is an alkyl sulfonate; the agent is a benzamide or an analogue or derivative thereof; the agent is a nicotinamide or an analogue or derivative thereof; the agent is a halogenated sugar or an analogue or derivative thereof; the agent is a DNA alkylating agent; the agent is an anti-microtubule agent; the agent is a topoisomerase inhibitor; the agent is a DNA cleaving agent; the agent is an antimetabolite; the agent inhibits adenosine deaminase; the agent inhibits purine ring synthesis; the agent is a nucleotide interconversion inhibitor; the agent inhibits dihydrofolate reduction; the agent blocks thymidine monophosphate; the agent causes DNA damage; the agent is a DNA intercalation agent; the agent is a RNA synthesis inhibitor; the agent is a pyrimidine synthesis inhibitor; the agent inhibits ribonucleotide synthesis or function; the agent inhibits thymidine monophosphate synthesis or function; the agent inhibits DNA synthesis; the agent causes DNA adduct formation; the agent inhibits protein synthesis; the agent inhibits microtubule function; the agent is a cyclin dependent protein kinase inhibitor; the agent is an epidermal growth factor kinase inhibitor; the agent is an elastase inhibitor; the agent is a factor Xa inhibitor; the agent is a farnesyltransferase inhibitor; the agent is a fibrinogen antagonist; the agent is a guanylate cyclase stimulant; the agent is a heat shock protein 90 antagonist; the agent is a heat shock protein 90 antagonist, wherein the heat shock protein 90 antagonist is geldanamycin or an analogue or derivative thereof; the agent is a guanylate cyclase stimulant; the agent is a HMGCoA reductase inhibitor; the agent is a HMGCoA reductase inhibitor, wherein the HMGCoA reductase inhibitor is simvastatin or an analogue or derivative thereof; the agent is a hydroorotate dehydrogenase inhibitor; the agent is an IKK2 inhibitor; the agent is an IL-1 antagonist; the agent is an ICE antagonist; the agent is an IRAK antagonist; the agent is an IL-4 agonist; the agent is an immunomodulatory agent; the agent is sirolimus or an analogue or derivative thereof; the agent is not sirolimus; the agent is everolimus or an analogue or derivative thereof; the agent is tacrolimus or an analogue or derivative thereof; the agent is not tacrolimus; the agent is biolmus or an analogue or derivative thereof; the agent is tresperimus or an analogue or derivative thereof; the agent is auranofin or an analogue or derivative thereof; the agent is 27-0-demethylrapamycin or an analogue or derivative thereof; the agent is gusperimus or an analogue or derivative thereof; the agent is pimecrolimus or an analogue or derivative thereof; the agent is ABT-578 or an analogue or derivative thereof; the agent is an inosine monophosphate dehydrogenase (IMPDH) inhibitor; the agent is an IMPDH inhibitor, wherein the IMPDH inhibitor is mycophenolic acid or an analogue or derivative thereof; the agent is an IMPDH inhibitor, wherein the IMPDH inhibitor is 1-alpha-25 dihydroxy vitamin D_3 or an analogue or derivative thereof; the agent is a leukotriene inhibitor; the agent is a MCP-1 antagonist; the agent is a MMP inhibitor; the agent is an NF kappa B inhibitor, the agent is an NF kappa B inhibitor, wherein the NF kappa B inhibitor is Bay 11-7082; the agent is an NO antagonist; the agent is a p38 MAP kinase inhibitor; the agent is a p38 MAP kinase inhibitor, wherein the p38 MAP kinase inhibitor is SB 202190; the agent is a phosphodiesterase inhibitor; the agent is a TGF beta inhibitor; the agent is a thromboxane A2 antagonist; the agent is a TNFα antagonist; the agent is a TACE inhibitor; the agent is a tyrosine kinase inhibitor; the agent is a vitronectin inhibitor; the agent is a fibroblast growth factor inhibitor; the agent is a protein kinase inhibitor; the agent is a PDGF receptor kinase inhibitor; the agent is an endothelial growth factor receptor kinase inhibitor; the agent is a retinoic acid receptor antagonist; the agent is a platelet derived growth factor receptor kinase inhibitor; the agent is a fibrinogen antagonist; the agent is an antimycotic agent; the agent is an antimycotic agent, wherein the antimycotic agent is sulconizole; the agent is a bisphosphonate; the agent is a phospholipase A1 inhibitor; the agent is a histamine H1/H2/H3 receptor antagonist; the agent is a macrolide antibiotic; the agent is a GPIIb/IIIa receptor antagonist; the agent is an endothelin receptor antagonist; the agent is a peroxisome proliferator-activated receptor agonist; the agent is an estrogen receptor agent; the agent is a somastostatin analogue; the agent is a neurokinin 1 antagonist; the agent is a neurokinin 3 antagonist; the agent is a VLA-4 antagonist; the agent is an osteoclast inhibitor; the agent is a DNA topoisomerase ATP hydrolyzing inhibitor; the agent is an angiotensin I converting enzyme inhibitor; the agent is an angiotensin II antagonist; the agent is an enkephalinase inhibitor; the agent is a peroxisome proliferator-activated receptor gamma agonist insulin sensitizer; the agent is a protein kinase C inhibitor; the agent is a ROCK (rho-associated kinase) inhibitor; the agent is a CXCR3 inhibitor; the agent is an ltk inhibitor; the agent is a cytosolic phospholipase A_2-alpha inhibitor; the agent is a PPAR agonist; the agent is an immunosuppressant; the agent is an Erb inhibitor; the agent is an apoptosis agonist; the agent is a lipocortin agonist; the agent is a VCAM-1 antagonist; the agent is a collagen antagonist; the agent is an alpha 2 integrin antagonist; the agent is a TNF alpha inhibitor; the agent is a nitric

oxide inhibitor; the agent is a cathepsin inhibitor; the agent is not an anti-inflammatory agent; the agent is not a steroid; the agent is not a glucocorticosteroid; the agent is not dexamethasone; the agent is not beclomethasone; the agent is not dipropionate; the agent is not an anti-infective agent; the agent is not an antibiotic; the agent is not an anti-fungal agent; the composition comprises a polymer; the composition comprises a polymer, and the polymer is, or comprises, a copolymer; the composition comprises a polymer, and the polymer is, or comprises, a block copolymer; the composition comprises a polymer, and the polymer is, or comprises, a random copolymer; the composition comprises a polymer, and the polymer is, or comprises, a biodegradable polymer; the composition comprises a polymer, and the polymer is, or comprises, a non-biodegradable polymer; the composition comprises a polymer, and the polymer is, or comprises, a hydrophilic polymer; the composition comprises a polymer, and the polymer is, or comprises, a hydrophobic polymer; the composition comprises a polymer, and the polymer is, or comprises, a polymer having hydrophilic domains; the composition comprises a polymer, and the polymer is, or comprises, a polymer having hydrophobic domains; the composition comprises a polymer, and the polymer is, or comprises, a non-conductive polymer; the composition comprises a polymer, and the polymer is, or comprises, an elastomer; the composition comprises a polymer, and the polymer is, or comprises, a hydrogel; the composition comprises a polymer, and the polymer is, or comprises, a silicone polymer; the composition comprises a polymer, and the polymer is, or comprises, a hydrocarbon polymer; the composition comprises a polymer, and the polymer is, or comprises, a styrene-derived polymer; the composition comprises a polymer, and the polymer is, or comprises, a butadiene-derived polymer; the composition comprises a polymer, and the polymer is, or comprises, a macromer; the composition comprises a polymer, and the polymer is, or comprises, a poly(ethylene glycol) polymer; the composition comprises a polymer, and the polymer is, or comprises, an amorphous polymer; the composition further comprises a second pharmaceutically active agent; the composition further comprises an anti-inflammatory agent; the composition further comprises an agent that inhibits infection; the composition further comprises an anthracycline; the composition further comprises doxorubicin; the composition further comprises mitoxantrone; the composition further comprises a fluoropyrimidine; the composition further comprises 5-fluorouracil (5-FU); the composition further comprises a folic acid antagonist; the composition further comprises methotrexate; the composition further comprises a podophylotoxin; the composition further comprises etoposide; the composition further comprises camptothecin; the composition further comprises a hydroxyurea; the composition further comprises a platinum complex; the composition further comprises cisplatin; the composition further comprises an anti-thrombotic agent; the composition further comprises a visualization agent; the composition further comprises a visualization agent, and the visualization agent is a radiopaque material, wherein the radiopaque material comprises a metal, a halogenated compound, or a barium containing compound; the composition further comprises a visualization agent, and the visualization agent is, or comprises, barium, tantalum, or technetium; the composition further comprises a visualization agent, and the visualization agent is, or comprises, an MRI responsive material; the composition further comprises a visualization agent, and the visualization agent is, or comprises, a gadolinium chelate; the composition further comprises a visualization agent, and the visualization agent is, or comprises, iron, magnesium, manganese, copper, or chromium; the composition further comprises a visualization agent, and the visualization agent is, or comprises, iron oxide compound; the composition further comprises a visualization agent, and the visualization agent is, or comprises, a dye, pigment, or colorant; the agent is released in effective concentrations from the composition comprising the agent by diffusion over a period ranging from the time of administration to about 90 days; the agent is released in effective concentrations from the composition comprising the agent by erosion of the composition over a period ranging from the time of administration to about 90 days; the composition further comprises an inflammatory cytokine; the composition further comprises an agent that stimulates cell proliferation; the composition further comprises a polymeric carrier; the composition is in the form of a gel, paste, or spray; the electrical device is partially constructed with the agent or the composition; the electrical device is impregnated with the agent or the composition; the agent or the composition forms a coating, and the coating directly contacts the electrical device; the agent or the composition forms a coating, and the coating indirectly contacts the electrical device; the agent or the composition forms a coating, and the coating partially covers the electrical device; the agent or the composition forms a coating, and the coating completely covers the electrical device; the agent or the composition is located within pores or holes of the electrical device; the agent or the composition is located within a channel, lumen, or divet of the electrical device; the electrical device further comprises an echogenic material; the electrical device further comprises an echogenic material, wherein the echogenic material is in the form of a coating; the electrical device is sterile; the agent is delivered from the electrical device, wherein the agent is released into tissue in the vicinity of the electrical device after deployment of the electrical device; the agent is delivered from the electrical device, wherein the agent is released into tissue in the vicinity of the electrical device after deployment of the electrical device, wherein the tissue is connective tissue; the agent is delivered from the electrical device, wherein the agent is released into tissue in the vicinity of the electrical device after deployment of the electrical device, wherein the tissue is muscle tissue; the agent is delivered from the electrical device, wherein the agent is released into tissue in the vicinity of the electrical device after deployment of the electrical device, wherein the tissue is nerve tissue; the agent is delivered from the electrical device, wherein the agent is released into tissue in the vicinity of the electrical device after deployment of the electrical device, wherein the tissue is epithelium tissue; the agent is delivered from the electrical device, wherein the agent is released in effective concentrations from the electrical device over a period ranging from the time of deployment of the electrical device to about 1 year; the agent is delivered from the electrical device, wherein the agent is released in effective concentrations from the electrical device over a period ranging from about 1 month to 6 months; the agent is delivered from the electrical device, wherein the agent is released in effective concentrations from the electrical device over a period ranging from about 1-90 days; the agent is delivered from the electrical device, wherein the agent is released in effec-

tive concentrations from the electrical device at a constant rate; the agent is delivered from the electrical device, wherein the agent is released in effective concentrations from the electrical device at an increasing rate; the agent is delivered from the electrical device, wherein the agent is released in effective concentrations from the electrical device at a decreasing rate; the agent is delivered from the electrical device, wherein the electrical device comprises about 0.01 μg to about 10 μg of the agent; the agent is delivered from the electrical device, wherein the electrical device comprises about 10 μg to about 10 mg of the agent; the agent is delivered from the electrical device, wherein the electrical device comprises about 10 mg to about 250 mg of the agent; the agent is delivered from the electrical device, wherein the electrical device comprises about 250 mg to about 1000 mg of the agent; the agent is delivered from the electrical device, wherein the electrical device comprises about 1000 mg to about 2500 mg of the agent; the agent is delivered from the electrical device, wherein a surface of the electrical device comprises less than 0.01 μg of the agent per mm^2 of electrical device surface to which the agent is applied; the agent is delivered from the electrical device, wherein a surface of the electrical device comprises about 0.01 μg to about 1 μg of the agent per mm^2 of electrical device surface to which the agent is applied; the agent is delivered from the electrical device, wherein a surface of the electrical device comprises about 1 μg to about 10 μg of the agent per mm^2 of electrical device surface to which the agent is applied; the agent is delivered from the electrical device, wherein a surface of the electrical device comprises about 10 μg to about 250 μg of the agent per mm^2 of electrical device surface to which the agent is applied; the agent is delivered from the electrical device, wherein a surface of the electrical device comprises about 250 μg to about 1000 μg of the agent per mm^2 of electrical device surface to which the agent is applied; the agent is delivered from the electrical device, wherein a surface of the electrical device comprises about 1000 μg to about 2500 μg of the agent per mm^2 of electrical device surface to which the agent is applied; the electrical device further comprises a coating, and the coating is a uniform coating; the electrical device further comprises a coating, and the coating is a non-uniform coating; the electrical device further comprises a coating, and the coating is a discontinuous coating; the electrical device further comprises a coating, and the coating is a patterned coating; the electrical device further comprises a coating, and the coating has a thickness of 100 μm or less; the electrical device further comprises a coating, and the coating has a thickness of 10 μm or less; the electrical device further comprises a coating, and the coating adheres to the surface of the electrical device upon deployment of the electrical device; the electrical device further comprises a coating, and the coating is stable at room temperature for a period of at least 1 year; the electrical device further comprises a coating, and the agent is present in the coating in an amount ranging between about 0.0001% to about 1% by weight; the electrical device further comprises a coating, and the agent is present in the coating in an amount ranging between about 1% to about 10% by weight; the electrical device further comprises a coating, and the agent is present in the coating in an amount ranging between about 10% to about 25% by weight; the electrical device further comprises a coating, and the agent is present in the coating in an amount ranging between about 25% to about 70% by weight; the electrical device further comprises a coating, and the coating comprises a polymer; the electrical device comprises a first coating having a first composition and a second coating having a second composition; the electrical device comprises a first coating having a first composition and a second coating having a second composition, wherein the first composition and the second composition are different; the agent or the composition is affixed to the electrical device; the agent or the composition is covalently attached to the electrical device; the agent or the composition is non-covalently attached to the electrical device; the electrical device comprises a coating that absorbs the agent or the composition; the electrical device is interweaved with a thread composed of, or coated with, the agent or the composition; a portion of the electrical device is covered with a sleeve that contains the agent or the composition; the electrical device is completely covered with a sleeve that contains the agent or the composition; a portion of the electrical device is covered with a mesh that contains the agent or the composition; the electrical device is completely covered with a mesh that contains the agent or the composition; the agent or the composition is applied to the electrical device surface prior to the placing of the electrical device into the host; the agent or the composition is applied to the electrical device surface during the placing of the electrical device into the host; the agent or the composition is applied to the electrical device surface immediately after the placing of the electrical device into the host; the agent or the composition is applied to the surface of the tissue in the host surrounding the electrical device prior to the placing of the electrical device into the host; the agent or the composition is applied to the surface of the tissue in the host surrounding the electrical device during the placing of the electrical device into the host; the agent or the composition is applied to the surface of the tissue in the host surrounding the electrical device immediately after the placing of the electrical device into the host; the agent or the composition is topically applied into the anatomical space where the electrical device is placed; and the agent or the composition is percutaneously injected into the tissue in the host surrounding the electrical device.

[0988] The present invention, in various aspects and embodiments, provides the following methods for making medical devices:

[0989] 1. Electrical Device

[0990] In one aspect, the present invention provides a method for making a medical device comprising: combining an electrical device and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the device and a host into which the device is implanted.

[0991] Such a method may be defined by one, two, or more of the following features: the electrical device is a neurostimulator; the electrical device is a spinal cord stimulator; the electrical device is a brain stimulator; the electrical device is a vagus nerve stimulator; the electrical device is a sacral nerve stimulator; the electrical device is a gastric nerve stimulator; the electrical device is an auditory nerve stimulator; the electrical device delivers stimulation to organs; the electrical device delivers stimulation to bone; the electrical device delivers stimulation to muscles; the electrical device delivers stimulation to tissues; the electrical

device is a device for continuous subarachnoid infusion; the electrical device is an implantable electrode; the electrical device is an implantable pulse generator; the electrical device is an electrical lead; the electrical device is a stimulation lead; the electrical device is a simulation catheter lead; the electrical device is cochlear implant; the electrical device is a microstimulator; the electrical device is battery powered; the electrical device is radio frequency powered; the electrical device is both battery and radio frequency powered; the electrical device is a cardiac rhythm management device; the electrical device is a cardiac pacemaker; the electrical device is an implantable cardioverter defibrillator system; the electrical device is a cardiac lead; the electrical device is a pacer lead; the electrical device is an endocardial lead; the electrical device is a cardioversion/defibrillator lead; the electrical device is an epicardial lead; the electrical device is an epicardial defibrillator lead; the electrical device is a patch defibrillator; the electrical device is a patch defibrillator lead; the electrical device is an electrical patch; the electrical device is a transvenous lead; the electrical device is an active fixation lead; the electrical device is a passive fixation lead; the electrical device is a sensing lead; the electrical device is a defibrillator; the electrical device is an implantable sensor; the electrical device is a left ventricular assist device; the electrical device is a pulse generator; the electrical device is a patch lead; the electrical device is an electrical patch; the electrical device is a cardiac stimulator; the electrical device is an electrical deviceable sensor; the electrical device is an electrical deviceable pump; the electrical device is a dural patch; the electrical device is a ventricular peritoneal shunt; the electrical device is a ventricular atrial shunt; the electrical device is adapted for treating or preventing epidural fibrosis post-laminectomy; the electrical device is adapted for treating or preventing cardiac rhythm abnormalities; the electrical device is adapted for treating or preventing atrial rhythm abnormalities; the electrical device is adapted for treating or preventing conduction abnormalities; the electrical device is adapted for treating or preventing ventricular rhythm abnormalities; the electrical device is adapted for treating or preventing pain; the electrical device is adapted for treating or preventing epilepsy; the electrical device is adapted for treating or preventing Parkinson's disease; the electrical device is adapted for treating or preventing movement disorders; the electrical device is adapted for treating or preventing obesity; the electrical device is adapted for treating or preventing depression; the electrical device is adapted for treating or preventing anxiety; the electrical device is adapted for treating or preventing hearing loss; the electrical device is adapted for treating or preventing ulcers; the electrical device is adapted for treating or preventing deep vein thrombosis; the electrical device is adapted for treating or preventing muscular atrophy; the electrical device is adapted for treating or preventing joint stiffness; the electrical device is adapted for treating or preventing muscle spasms; the electrical device is adapted for treating or preventing osteoporosis; the electrical device is adapted for treating or preventing scoliosis; the electrical device is adapted for treating or preventing spinal disc degeneration; the electrical device is adapted for treating or preventing spinal cord injury; the electrical device is adapted for treating or preventing urinary dysfunction; the electrical device is adapted for treating or preventing gastroparesis; the electrical device is adapted for treating or preventing malignancy; the electrical device is adapted for treating or preventing arachnoiditis; the electrical device is adapted for treating or preventing chronic disease; the electrical device is adapted for treating or preventing migraine; the electrical device is adapted for treating or preventing sleep disorders; the electrical device is adapted for treating or preventing dementia; and the electrical device is adapted for treating or preventing Alzheimer's disease.

[0992] 2. Neurostimulator for Treating Chronic Pain

[0993] In one aspect, the present invention provides a method for making a medical device comprising: combining a neurostimulator for treating chronic pain (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the device and a host into which the device is implanted.

[0994] Such a method may be further defined by one, two, or more of the following features: the chronic pain results from injury; the chronic pain results from an illness; the chronic pain results from scoliosis; the chronic pain results from spinal disc degeneration; the chronic pain results from malignancy; the chronic pain results from arachnoiditis; the chronic pain results from a chronic disease; the chronic pain results from a pain syndrome; the neurostimulator comprises a lead that delivers electrical stimulation to a nerve and an electrical connection that connects a power source to the lead; the neurostimulator is adapted for spinal cord stimulation, and comprises a sensor that detects the position of the spine and a stimulator that emits pulses that decrease in amplitude when the back is in a supine position; the neurostimulator comprises an electrode and a control circuit that generates pulses and rest period based on intervals corresponding to the host body's activity and regeneration period; the neurostimulator comprises a stimulation catheter lead and an electrode; and the neurostimulator is a self-centering epidural spinal cord lead.

[0995] 3. Neurostimulator for Treating Parkinson's Disease

[0996] In one aspect, the present invention provides a method for making a medical device comprising: combining a neurostimulator for treating Parkinson's Disease (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the device and a host into which the device is implanted.

[0997] In certain embodiments, the neurostimulator comprises an intracranially implantable electrical control module and an electrode. In other embodiments, the neurostimulator comprises a sensor and an electrode.

[0998] 4. Vagal Nerve Stimulator for Treating Epilepsy

[0999] In one aspect, the present invention provides a method for making a medical device comprising: combining a vagal nerve stimulator for treating epilepsy (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the device and a host into which the device is implanted.

[1000] 5. Vagal Nerve Stimulator for Treating Other Disorders

[1001] In one aspect, the present invention provides a method for making a medical device comprising: combining a vagal nerve stimulator (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the device and a host into which the device is implanted.

[1002] Such a method may be further defined by one, two or more of the following features: the vagal nerve stimulator is adapted for treating or preventing depression; the vagal nerve stimulator is adapted for treating or preventing anxiety; the vagal nerve stimulator is adapted for treating or preventing panic disorders; the vagal nerve stimulator is adapted for treating or preventing obsessive-compulsive disorders; the vagal nerve stimulator is adapted for treating or preventing post-traumatic disorders; the vagal nerve stimulator is adapted for treating or preventing obesity; the vagal nerve stimulator is adapted for treating or preventing migraine; the vagal nerve stimulator is adapted for treating or preventing sleep disorders; the vagal nerve stimulator is adapted for treating or preventing dementia; the vagal nerve stimulator is adapted for treating or preventing Alzheimer's disease; and the vagal nerve stimulator is adapted for treating or preventing chronic or degenerative neurological disorders.

[1003] 6. Sacral Nerve Stimulator

[1004] In one aspect, the present invention provides a method for making a medical device comprising: combining a sacral nerve stimulator for treating a bladder control problem (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the device and a host into which the device is implanted.

[1005] Such a method may be further defined by one, two, or more of the following features: the sacral nerve stimulator is adapted for treating or preventing urge incontinence; the sacral nerve stimulator is adapted for treating or preventing nonobstructive urinary retention; the sacral nerve stimulator is adapted for treating or preventing urgency frequency; the sacral nerve stimulator is an intramuscular electrical stimulator; and the sacral nerve stimulator is a leadless, tubular-shaped microstimulator.

[1006] 7. Gastric Nerve Stimulator

[1007] In one aspect, the present invention provides a method for making a medical device comprising: combining a gastric nerve stimulator for treating a astrointestinal disorder (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the device and a host into which the device is implanted.

[1008] Such a method may be further defined by one, two, or more of the following features: the gastric nerve stimulator is adapted for treating or preventing morbid obesity; the gastric nerve stimulator is adapted for treating or preventing constipation; the gastric nerve stimulator comprises an electrical lead, an electrode and a stimulation generator; and the gastric nerve stimulator comprises an electrical signal controller, connector wire and an attachment lead.

[1009] 8. Cochlear Implant

[1010] The present invention provides a method for making a medical device comprising: combining a cochlear implant for treating deafness (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the device and a host into which the device is implanted.

[1011] Such a method may be further defined by one, two or more the following features: the cochlear implant comprises a plurality of transducer elements; the cochlear implant comprises a sound-to-electrical stimulation encoder, a body implantable receiver-stimulator, and electrodes; the cochlear implant comprises a transducer and an electrode array; and the cochlear implant is a subcranially implantable electomechanical system.

[1012] 9. Bone Growth Stimulator

[1013] In one aspect, the present invention provides a method for making a medical device comprising: combining a bone growth stimulator (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the device and a host into which the device is implanted.

[1014] In certain embodiments, the bone growth stimulator comprises an electrode and a generator having a strain response piezoelectric material that responds to strain.

[1015] 10. Cardiac Pacemaker

[1016] In one aspect, the present invention provides a method for making a medical device comprising: combining a cardiac pacemaker (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the device and a host into which the device is implanted.

[1017] In certain embodiments, the cardiac pacemaker is an adaptive rate pacemaker. In certain other embodiments, the cardiac pacemaker is a rate responsive pacemaker.

[1018] 11. Implantable Cardioverter Defibrillator

[1019] In one aspect, the present invention provides a method for making a medical device comprising: combining an implantable cardioverter defibrillator (ICD) system (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the device and a host into which the device is implanted.

[1020] Such a method may be further defined by one, two, or more of the following features: the implantable cardioverter defibrillator is adapted for treating tachyarraythmias; the implantable cardioverter defibrillator is adapted for ventricular tachycardia; the implantable cardioverter defibrillator is adapted for treating ventricular fibrillation; the implantable cardioverter defibrillator is adapted for treating atrial tachycardia; the implantable cardioverter defibrillator is adapted for treating atrial fibrillation; the implantable cardioverter defibrillator is adapted for treating arrhythmias.

[1021] 12. Vagus Nerve Stimulator for Treating Arrhythemia

[1022] In one aspect, the present invention provides a method for making a medical device comprising: combining

a vagus nerve stimulator for treating arrhythemia (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the device and a host into which the device is implanted.

[1023] Such a method may be further defined by one, two or more of the following features: the vagus nerve stimulator is adapted for treating supraventricular arrhythmias; the vagus nerve stimulator is adapted for treating angina pectoris; the vagus nerve stimulator is adapted for treating atrial tachycardia; the vagus nerve stimulator is adapted for treating atrial flutter; the vagus nerve stimulator is adapted for treating arterial fibrillation; the vagus nerve stimulator is arrhythmias that result in low cardiac output; and the vagus nerve stimulator comprises a programmable pulse generator.

[1024] 13. Electrical Lead

[1025] In one aspect, the present invention provides a method for making a medical device comprising: combining an electrical lead (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the device and a host into which the device is implanted.

[1026] Such a method may be further defined by one, two or more of the following features: the electrical lead comprises a connector assembly, a conductor and an electrode; the electrical lead is unipolar; the electrical lead is bipolar; the electrical lead is tripolar; the electrical lead is quadripolar; the electrical lead comprises an insulating sheath; the electrical lead is a medical lead; the electrical lead is a cardiac lead; the electrical lead is a pacer lead; the electrical lead is a pacing lead; the electrical lead is a pacemaker lead; the electrical lead is an endocardial lead; the electrical lead is an endocardial pacing lead; the electrical lead is a cardioversion lead; the electrical lead is an epicardial lead; the electrical lead is an epicardial defibrillator lead; the electrical lead is a patch defibrillator; the electrical lead is a patch lead; the electrical lead is an electrical patch; the electrical lead is a transvenous lead; the electrical lead is an active fixation lead; the electrical lead is a passive fixation lead; the electrical lead is a sensing lead; the electrical lead is expandable; the electrical lead has a coil configuration; and the electrical lead has an active fixation element for attachment to host tissue.

[1027] 14. Neurostimulator

[1028] In one aspect, the present invention provides a method for making a medical device comprising: combining a neurostimulator (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the device and a host into which the device is implanted.

[1029] Such a method may be further defined by one, two or more of the following features: the electrical device is a neurostimulator; the electrical device is a spinal cord stimulator; the electrical device is a brain stimulator; the electrical device is a vagus nerve stimulator; the electrical device is a sacral nerve stimulator; the electrical device is a gastric nerve stimulator; the electrical device is an auditory nerve stimulator; the electrical device delivers stimulation to organs; the electrical device delivers stimulation to bone; the electrical device delivers stimulation to muscles; the electrical device delivers stimulation to tissues; the electrical device is a device for continuous subarachnoid infusion; the electrical device is an implantable electrode; the electrical device is an electrical lead; the electrical device is a simulation catheter lead; the electrical device is cochlear implant; the electrical device is a microstimulator; the electrical device is battery powered; the electrical device is radio frequency powered; the electrical device is both battery and radio frequency powered; the electrical device is adapted for treating or preventing pain; the electrical device is adapted for treating or preventing epilepsy; the electrical device is adapted for treating or preventing Parkinson's disease; the electrical device is adapted for treating or preventing movement disorders; the electrical device is adapted for treating or preventing obesity; the electrical device is adapted for treating or preventing depression; the electrical device is adapted for treating or preventing anxiety; the electrical device is adapted for treating or preventing hearing loss; the electrical device is adapted for treating or preventing ulcers; the electrical device is adapted for treating or preventing deep vein thrombosis; the electrical device is adapted for treating or preventing muscular atrophy; the electrical device is adapted for treating or preventing joint stiffness; the electrical device is adapted for treating or preventing muscle spasms; the electrical device is adapted for treating or preventing osteoporosis; the electrical device is adapted for treating or preventing scoliosis; the electrical device is adapted for treating or preventing spinal disc degeneration; the electrical device is adapted for treating or preventing spinal cord injury; the electrical device is adapted for treating or preventing urinary dysfunction; the electrical device is adapted for treating or preventing gastroparesis; the electrical device is adapted for treating or preventing malignancy; the electrical device is adapted for treating or preventing arachnoiditis; the electrical device is adapted for treating or preventing chronic disease; the electrical device is adapted for treating or preventing migraine; the electrical device is adapted for treating or preventing sleep disorders; the electrical device is adapted for treating or preventing dementia; and the electrical device is adapted for treating or preventing Alzheimer's disease.

[1030] 15. Cardiac Rhythm Management Device

[1031] In one aspect, the present invention provides a method for making a medical device comprising: combining a cardiac rhythm management device (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the device and a host into which the device is implanted.

[1032] Such a method may be defined by one, two or more of the following features: the electrical device is an implantable pulse generator; the electrical device is an electrical lead; the electrical device is a stimulation lead; the electrical device is a simulation catheter lead; the electrical device is a microstimulator; the electrical device is battery powered; the electrical device is radio frequency powered; the electrical device is both battery and radio frequency powered; the electrical device is a cardiac pacemaker; the electrical device is an implantable cardioverter defibrillator system; the electrical device is a cardiac lead; the electrical device is a pacer lead; the electrical device is an endocardial lead; the electrical device is a cardioversion/defibrillator lead; the electrical device is an epicardial lead; the electrical device is an epicardial defibrillator lead; the electrical device is a

patch defibrillator; the electrical device is a patch defibrillator lead; the electrical device is an electrical patch; the electrical device is a transvenous lead; the electrical device is an active fixation lead; the electrical device is a passive fixation lead; the electrical device is a sensing lead; the electrical device is a defibrillator; the electrical device is an implantable sensor; the electrical device is a left ventricular assist device; the electrical device is a pulse generator; the electrical device is a patch lead; the electrical device is an electrical patch; the electrical device is a cardiac stimulator; the electrical device is an electrical deviceable sensor; the electrical device is an electrical deviceable pump; the electrical device is a dural patch; the electrical device is a ventricular peritoneal shunt; the electrical device is a ventricular atrial shunt; the electrical device is adapted for treating or preventing epidural fibrosis post-laminectomy; the electrical device is adapted for treating or preventing cardiac rhythm abnormalities; the electrical device is adapted for treating or preventing atrial rhythm abnormalities; the electrical device is adapted for treating or preventing conduction abnormalities; and the electrical device is adapted for treating or preventing ventricular rhythm abnormalities.

[**1033**] In certain embodiments, the combining comprises (a) assembling or providing an electrical lead having an electrode; (b) mixing an anti-scarring agent with an organic solvent to form a solution; (c) applying the solution to the electrical lead; and (d) drying the solution on the electrical lead to remove the organic solvent.

[**1034**] In certain embodiments, the combining comprises (a) assembling or providing an electrical lead having an electrode; (b) mixing an anti-scarring agent with an organic solvent to form a solution; (c) applying the solution to the electrode; and (d) drying the solution on the lead to remove the organic solvent.

[**1035**] In certain embodiments, the combining comprises (a) assembling or providing an electrical lead having a porous electrode tip; (b) mixing an anti-scarring agent with an organic solvent to form a solution; (c) applying the solution to the porous electrode tip; and (d) drying the solution on the electrical lead to remove the organic solvent.

[**1036**] In certain embodiments, the combining comprises (a) assembling or providing an electrical lead having an electrode; (b) mixing an anti-scarring agent with an organic solvent to form a solution; (c) applying the solution to the electrical lead; (d) drying the solution on the electrical lead to remove the organic solvent; and (e) sterilizing the electrical lead resulting from (d).

[**1037**] In certain embodiments, the combining comprises (a) assembling or providing an electrical lead having an electrode; (b) mixing an anti-scarring agent with an organic solvent to form a solution; (c) applying the solution to the electrode; (d) drying the solution on the lead to remove the organic solvent; and (e) sterilizing the electrical lead resulting from (d).

[**1038**] In certain embodiments, the combining comprises (a) assembling or providing an electrical lead having a porous electrode tip; (b) mixing an anti-scarring agent with an organic solvent to form a solution; (c) applying the solution to the porous electrode tip; (d) drying the solution on the electrical lead to remove the organic solvent; and (e) sterilizing the electrical lead resulting from (d).

[**1039**] In certain embodiments, the combining comprises (a) assembling or providing an electrical lead having an electrode; (b) mixing an anti-scarring agent with an organic solvent to form a solution; (c) applying the solution to the electrical lead; (d) drying the solution on the electrical lead to remove the organic solvent; (e) packaging the lead resulting from (d); and (f) sterilizing the packaged lead resulted from (e).

[**1040**] In certain embodiments, the combining comprises (a) assembling or providing an electrical lead having an electrode; (b) mixing an anti-scarring agent with an organic solvent to form a solution; (c) applying the solution to the electrode; (d) drying the solution on the lead to remove the organic solvent; (e) packaging the lead; and (f) sterilizing the packaged lead resulting from (e).

[**1041**] In certain embodiments, the combining comprises (a) assembling or providing an electrical lead having a porous electrode tip; (b) mixing an anti-scarring agent with an organic solvent to form a solution; (c) applying the solution to the porous electrode tip; (d) drying the solution on the electrical lead to remove the organic solvent; (e) packaging the electrical lead resulting from (d); and (f) sterilizing the packaged electrical lead resulting from (e).

[**1042**] In certain embodiments, the combining comprises (a) assembling or providing an electrical lead having an electrode; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the lead; and (e) drying the solution on the electrical lead to remove the organic solvent.

[**1043**] In certain embodiments, the combining comprises (a) assembling or providing an electrical lead having an electrode; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the electrode; and (d) drying the solution on the electrical lead to remove the organic solvent.

[**1044**] In certain embodiments, the combining comprises: (a) assembling or providing an electrical lead having a porous electrode tip; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the porous electrode tip; and (d) drying the solution on the electrical lead to remove the organic solvent.

[**1045**] In certain embodiments, the combining comprises: (a) assembling or providing a lead having an electrode; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the electrical lead; (d) drying the solution on the lead to remove the organic solvent; and (e) sterilizing the electrical lead resulting from (d).

[**1046**] In certain embodiments, the combining comprises: (a) assembling or providing an electrical lead having an electrode; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the electrode; (d) drying the solution on the electrical lead to remove the organic solvent; and (e) sterilizing the electrical lead resulting from (d).

[**1047**] In certain embodiments, the combining comprises: (a) assembling or providing an electrical lead having a

porous electrode tip; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the porous electrode tip; (d) drying the solution on the electrical lead to remove the organic solvent; and (e) sterilizing the electrical lead resulting from (d).

[1048] In certain embodiments, the combining comprises: (a) assembling or providing a lead having an electrode; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the electrical lead; (d) drying the solution on the lead to remove the organic solvent; (e) packaging the electrical lead resulting from (d); and (f) sterilizing the packaged electrical lead resulting from (e).

[1049] In certain embodiments, the combining comprises: (a) assembling or providing an electrical lead having an electrode; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the electrode; (d) drying the solution on the electrical lead to remove the organic solvent; (e) packaging the electrical lead resulting from (d); and (f) sterilizing the packaged electrical lead resulting from (e).

[1050] In certain embodiments, the combining comprises: (a) assembling or providing an electrical lead having a porous electrode tip; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the porous electrode tip; (d) drying the solution on the electrical lead to remove the organic solvent; (e) packaging the electrical lead resulting from (d); and (f) sterilizing the packaged electrical lead resulting from (e).

[1051] In certain embodiments, the combining comprises (a) assembling or providing an electrical lead having an electrode; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the lead; and (d) drying the solution on the electrical lead to remove the organic solvent; and wherein the anti-inflammatory agent is a steroid.

[1052] In certain embodiments, the combining comprises (a) assembling or providing an electrical lead having an electrode; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the electrode; and (d) drying the solution on the electrical lead to remove the organic solvent; and wherein the anti-inflammatory agent is a steroid.

[1053] In certain embodiments, the combining comprises: (a) assembling or providing an electrical lead having a porous electrode tip; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the porous electrode tip; and (d) drying the solution on the electrical lead to remove the organic solvent; and wherein the anti-inflammatory agent is a steroid.

[1054] In certain embodiments, the combining comprises: (a) assembling or providing a lead having an electrode; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the electrical lead; (d) drying the solution on the lead to remove the organic solvent; and (e) sterilizing the electrical lead resulting from (d); and wherein the anti-inflammatory agent is a steroid.

[1055] In certain embodiments, the combining comprises: (a) assembling or providing an electrical lead having an electrode; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the electrode; (d) drying the solution on the electrical lead to remove the organic solvent; and (e) sterilizing the electrical lead resulting from (d); and wherein the anti-inflammatory agent is a steroid.

[1056] In certain embodiments, the combining comprises: (a) assembling or providing an electrical lead having a porous electrode tip; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the porous electrode tip; (d) drying the solution on the electrical lead to remove the organic solvent; and (e) sterilizing the electrical lead resulting from (d); and wherein the anti-inflammatory agent is a steroid.

[1057] In certain embodiments, the combining comprises: (a) assembling or providing a lead having an electrode; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the electrical lead; (d) drying the solution on the lead to remove the organic solvent; (e) packaging the electrical lead resulting from (d); and (f) sterilizing the packaged electrical lead resulting from (e); and wherein the anti-inflammatory agent is a steroid.

[1058] In certain embodiments, the combining comprises: (a) assembling or providing an electrical lead having an electrode; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the electrode; (d) drying the solution on the electrical lead to remove the organic solvent; (e) packaging the electrical lead resulting from (d); and (f) sterilizing the packaged electrical lead resulting from (e); and wherein the anti-inflammatory agent is a steroid.

[1059] In certain embodiments, the combining comprises: (a) assembling or providing an electrical lead having a porous electrode tip; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the porous electrode tip; (d) drying the solution on the electrical lead to remove the organic solvent; (e) packaging the electrical lead resulting from (d); and (f) sterilizing the packaged electrical lead resulting from (e); and wherein the anti-inflammatory agent is a steroid.

[1060] In certain embodiments, the combining comprises (a) assembling or providing an electrical lead having an electrode; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the lead; and (d) drying the solution on the electrical lead to remove the organic solvent; and wherein the anti-inflammatory is selected from the group consisting of medrysone, desoximetasone, triamcinolone, fluoromethalone, flurandrenolide, halcinonide, betamethasone benzoate, triamicinolone acetonide, diflorasone diacetate, betamethasone valerate, dexamethasone, and beclomethasone dipropionate anhydrous.

[1061] In certain embodiments, the combining comprises (a) assembling or providing an electrical lead having an electrode; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the electrode; and (d) drying the solution on the electrical lead to remove the organic solvent; and wherein the anti-inflammatory is selected from the group consisting of medrysone, desoximetasone, triamcinolone, fluoromethalone, flurandrenolide, halcinonide, betamethasone benzoate, triamicinolone acetonide, diflorasone diacetate, betamethasone valerate, dexamethasone, and beclomethasone dipropionate anhydrous.

[1062] In certain embodiments, the combining comprises: (a) assembling or providing an electrical lead having a porous electrode tip; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the porous electrode tip; and (d) drying the solution on the electrical lead to remove the organic solvent; and wherein the anti-inflammatory is selected from the group consisting of medrysone, desoximetasone, triamcinolone, fluoromethalone, flurandrenolide, halcinonide, betamethasone benzoate, triamicinolone acetonide, diflorasone diacetate, betamethasone valerate, dexamethasone, and beclomethasone dipropionate anhydrous.

[1063] In certain embodiments, the combining comprises: (a) assembling or providing a lead having an electrode; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the electrical lead; (d) drying the solution on the lead to remove the organic solvent; and (e) sterilizing the electrical lead resulting from (d); and wherein the anti-inflammatory is selected from the group consisting of medrysone, desoximetasone, triamcinolone, fluoromethalone, flurandrenolide, halcinonide, betamethasone benzoate, triamicinolone acetonide, diflorasone diacetate, betamethasone valerate, dexamethasone, and beclomethasone dipropionate anhydrous.

[1064] In certain embodiments, the combining comprises: (a) assembling or providing an electrical lead having an electrode; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the electrode; (d) drying the solution on the electrical lead to remove the organic solvent; and (e) sterilizing the electrical lead resulting from (d); and wherein the anti-inflammatory is selected from the group consisting of medrysone, desoximetasone, triamcinolone, fluoromethalone, flurandrenolide, halcinonide, betamethasone benzoate, triamicinolone acetonide, diflorasone diacetate, betamethasone valerate, dexamethasone, and beclomethasone dipropionate anhydrous.

[1065] In certain embodiments, the combining comprises: (a) assembling an electrical lead having a porous electrode tip; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the porous electrode tip; (d) drying the solution on the electrical lead to remove the organic solvent; and (e) sterilizing the electrical lead resulting from (d); and wherein the anti-inflammatory is selected from the group consisting of medrysone, desoximetasone, triamcinolone, fluoromethalone, flurandrenolide, halcinonide, betamethasone benzoate, triamicinolone acetonide, diflorasone diacetate, betamethasone valerate, dexamethasone, and beclomethasone dipropionate anhydrous.

[1066] In certain embodiments, the combining comprises: (a) assembling or providing a lead having an electrode; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the electrical lead; (d) drying the solution on the lead to remove the organic solvent; (e) packaging the electrical lead resulting from (d); and (f) sterilizing the packaged electrical lead resulting from (e); and wherein the anti-inflammatory is selected from the group consisting of medrysone, desoximetasone, triamcinolone, fluoromethalone, flurandrenolide, halcinonide, betamethasone benzoate, triamicinolone acetonide, diflorasone diacetate, betamethasone valerate, dexamethasone, and beclomethasone dipropionate anhydrous.

[1067] In certain embodiments, the combining comprises: (a) assembling or providing an electrical lead having an electrode; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the electrode; (d) drying the solution on the electrical lead to remove the organic solvent; (e) packaging the electrical lead resulting from (d); and (f) sterilizing the packaged electrical lead resulting from (e); and wherein the anti-inflammatory is selected from the group consisting of medrysone, desoximetasone, triamcinolone, fluoromethalone, flurandrenolide, halcinonide, betamethasone benzoate, triamicinolone acetonide, diflorasone diacetate, betamethasone valerate, dexamethasone, and beclomethasone dipropionate anhydrous.

[1068] In certain embodiments, the combining comprises: (a) assembling or providing an electrical lead having a porous electrode tip; (b) mixing an anti-scarring agent and an anti-inflammatory agent with an organic solvent to form a solution; (c) applying the solution to the porous electrode tip; (d) drying the solution on the electrical lead to remove the organic solvent; (e) packaging the electrical lead resulting from (d); and (f) sterilizing the packaged electrical lead resulting from (e); and wherein the anti-inflammatory is selected from the group consisting of medrysone, desoximetasone, triamcinolone, fluoromethalone, flurandrenolide, halcinonide, betamethasone benzoate, triamicinolone acetonide, diflorasone diacetate, betamethasone valerate, dexamethasone, and beclomethasone dipropionate anhydrous.

[1069] Additional Features Related to Methods for Inhibiting Scarring

[1070] The methods for making medical devices as described above may also be further defined by one, two, or more of the following features: the agent inhibits cell regeneration; the agent inhibits angiogenesis; the agent inhibits fibroblast migration; the agent inhibits fibroblast proliferation; the agent inhibits deposition of extracellular matrix; the agent inhibits tissue remodeling; the agent is an angiogenesis inhibitor; the agent is a 5-lipoxygenase inhibitor or antagonist; the agent is a chemokine receptor antagonist; the agent is a cell cycle inhibitor; the agent is a taxane; the agent is an anti-microtubule agent; the agent is paclitaxel; the agent is not paclitaxel; the agent is an analogue or derivative of paclitaxel; the agent is a vinca alkaloid; the

agent is camptothecin or an analogue or derivative thereof; the agent is a podophyllotoxin; the agent is a podophyllotoxin, wherein the podophyllotoxin is etoposide or an analogue or derivative thereof; the agent is an anthracycline; the agent is an anthracycline, wherein the anthracycline is doxorubicin or an analogue or derivative thereof; the agent is an anthracycline, wherein the anthracycline is mitoxantrone or an analogue or derivative thereof; the agent is a platinum compound; the agent is a nitrosourea; the agent is a nitroimidazole; the agent is a folic acid antagonist; the agent is a cytidine analogue; the agent is a pyrimidine analogue; the agent is a fluoropyrimidine analogue; the agent is a purine analogue; the agent is a nitrogen mustard or an analogue or derivative thereof; the agent is a hydroxyurea; the agent is a mytomicin or an analogue or derivative thereof; the agent is an alkyl sulfonate; the agent is a benzamide or an analogue or derivative thereof; the agent is a nicotinamide or an analogue or derivative thereof; the agent is a halogenated sugar or an analogue or derivative thereof; the agent is a DNA alkylating agent; the agent is an anti-microtubule agent; the agent is a topoisomerase inhibitor; the agent is a DNA cleaving agent; the agent is an antimetabolite; the agent inhibits adenosine deaminase; the agent inhibits purine ring synthesis; the agent is a nucleotide interconversion inhibitor; the agent inhibits dihydrofolate reduction; the agent blocks thymidine monophosphate; the agent causes DNA damage; the agent is a DNA intercalation agent; the agent is a RNA synthesis inhibitor; the agent is a pyrimidine synthesis inhibitor; the agent inhibits ribonucleotide synthesis or function; the agent inhibits thymidine monophosphate synthesis or function; the agent inhibits DNA synthesis; the agent causes DNA adduct formation; the agent inhibits protein synthesis; the agent inhibits microtubule function; the agent is a cyclin dependent protein kinase inhibitor; the agent is an epidermal growth factor kinase inhibitor; the agent is an elastase inhibitor; the agent is a factor Xa inhibitor; the agent is a farnesyltransferase inhibitor; the agent is a fibrinogen antagonist; the agent is a guanylate cyclase stimulant; the agent is a heat shock protein 90 antagonist; the agent is a heat shock protein 90 antagonist, wherein the heat shock protein 90 antagonist is geldanamycin or an analogue or derivative thereof; the agent is a guanylate cyclase stimulant; the agent is a HMGCoA reductase inhibitor; the agent is a HMGCoA reductase inhibitor, wherein the HMGCoA reductase inhibitor is simvastatin or an analogue or derivative thereof; the agent is a hydroorotate dehydrogenase inhibitor; the agent is an IKK2 inhibitor; the agent is an IL-1 antagonist; the agent is an ICE antagonist; the agent is an IRAK antagonist; the agent is an IL-4 agonist; the agent is an immunomodulatory agent; the agent is sirolimus or an analogue or derivative thereof; the agent is not sirolimus; the agent is everolimus or an analogue or derivative thereof; the agent is tacrolimus or an analogue or derivative thereof; the agent is not tacrolimus; the agent is biolmus or an analogue or derivative thereof; the agent is tresperimus or an analogue or derivative thereof; the agent is auranofin or an analogue or derivative thereof; the agent is 27-0-demethylrapamycin or an analogue or derivative thereof; the agent is gusperimus or an analogue or derivative thereof; the agent is pimecrolimus or an analogue or derivative thereof; the agent is ABT-578 or an analogue or derivative thereof; the agent is an inosine monophosphate dehydrogenase (IMPDH) inhibitor; the agent is an IMPDH inhibitor, wherein the IMPDH inhibitor is mycophenolic acid or an analogue or derivative thereof; the agent is an IMPDH inhibitor, wherein the IMPDH inhibitor is 1-alpha-25 dihydroxy vitamin D_3 or an analogue or derivative thereof; the agent is a leukotriene inhibitor; the agent is a MCP-1 antagonist; the agent is a MMP inhibitor; the agent is an NF kappa B inhibitor; the agent is an NF kappa B inhibitor, wherein the NF kappa B inhibitor is Bay 11-7082; the agent is an NO antagonist; the agent is a p38 MAP kinase inhibitor; the agent is a p38 MAP kinase inhibitor, wherein the p38 MAP kinase inhibitor is SB 202190; the agent is a phosphodiesterase inhibitor; the agent is a TGF beta inhibitor; the agent is a thromboxane A2 antagonist; the agent is a TNF alpha antagonist; the agent is a TACE inhibitor; the agent is a tyrosine kinase inhibitor; the agent is a vitronectin inhibitor; the agent is a fibroblast growth factor inhibitor; the agent is a protein kinase inhibitor; the agent is a PDGF receptor kinase inhibitor; the agent is an endothelial growth factor receptor kinase inhibitor; the agent is a retinoic acid receptor antagonist; the agent is a platelet derived growth factor receptor kinase inhibitor; the agent is a fibrinogen antagonist; the agent is an antimycotic agent; the agent is an antimycotic agent, wherein the antimycotic agent is sulconizole; the agent is a bisphosphonate; the agent is a phospholipase A1 inhibitor; the agent is a histamine H1/H2/H3 receptor antagonist; the agent is a macrolide antibiotic; the agent is a GPIIb/IIIa receptor antagonist; the agent is an endothelin receptor antagonist; the agent is a peroxisome proliferator-activated receptor agonist; the agent is an estrogen receptor agent; the agent is a somastostatin analogue; the agent is a neurokinin 1 antagonist; the agent is a neurokinin 3 antagonist; the agent is a VLA-4 antagonist; the agent is an osteoclast inhibitor; the agent is a DNA topoisomerase ATP hydrolyzing inhibitor; the agent is an angiotensin I converting enzyme inhibitor; the agent is an angiotensin II antagonist; the agent is an enkephalinase inhibitor; the agent is a peroxisome proliferator-activated receptor gamma agonist insulin sensitizer; the agent is a protein kinase C inhibitor; the agent is a ROCK (rho-associated kinase) inhibitor; the agent is a CXCR3 inhibitor; the agent is an ltk inhibitor; the agent is a cytosolic phospholipase A_2-alpha inhibitor; the agent is a PPAR agonist; the agent is an immunosuppressant; the agent is an Erb inhibitor; the agent is an apoptosis agonist; the agent is a lipocortin agonist; the agent is a VCAM-1 antagonist; the agent is a collagen antagonist; the agent is an alpha 2 integrin antagonist; the agent is a TNF alpha inhibitor; the agent is a nitric oxide inhibitor, the agent is a cathepsin inhibitor; the agent is not an anti-inflammatory agent; the agent is not a steroid; the agent is not a glucocorticosteroid; the agent is not dexamethasone; the agent is not beclomethasone; the agent is not dipropionate; the agent is not an anti-infective agent; the agent is not an antibiotic; the agent is not an anti-fungal agent; the composition comprises a polymer; the composition comprises a polymeric carrier; the anti-scarring agent inhibits adhesion between the medical device and a host into which the medical device is implanted; the medical device delivers the anti-scarring agent locally to tissue proximate to the medical device; the medical device has a coating that comprises the anti-scarring agent; the medical device has a coating that comprises the agent and is disposed on a surface of the electrical device; the medical device has a coating that comprises the agent and directly contacts the electrical device; the medical device has a coating that comprises the agent and indirectly contacts the electrical device; the medi-

cal device has a coating that comprises the agent and partially covers the electrical device; the medical device has a coating that comprises the agent and completely covers the electrical device; the medical device has a uniform coating; the medical device has a non-uniform coating; the medical device has a discontinuous coating; the medical device has a patterned coating; the medical device has a coating with a thickness of 100 μm or less; the medical device has a coating with a thickness of 10 μm or less; the medical device has a coating, and the coating adheres to the surface of the electrical device upon deployment of the electrical device; the medical device has a coating, and wherein the coating is stable at room temperature for a period of 1 year; the medical device has a coating, and wherein the anti-scarring agent is present in the coating in an amount ranging between about 0.0001% to about 1% by weight; the medical device has a coating, and wherein the anti-scarring agent is present in the coating in an amount ranging between about 1% to about 10% by weight; the medical device has a coating, and wherein the anti-scarring agent is present in the coating in an amount ranging between about 10% to about 25% by weight; the medical device has a coating, and wherein the anti-scarring agent is present in the coating in an amount ranging between about 25% to about 70% by weight; the medical device has a coating, and wherein the coating further comprises a polymer; the medical device has a first coating having a first composition and a second coating having a second composition; the medical device has a first coating having a first composition and a second coating having a second composition, wherein the first composition and the second composition are different; the composition comprises a polymer; the composition comprises a polymeric carrier; the composition comprises a polymeric carrier, and wherein the polymeric carrier comprises a copolymer; the composition comprises a polymeric carrier, and wherein the polymeric carrier comprises a block copolymer; the composition comprises a polymeric carrier, and wherein the polymeric carrier comprises a random copolymer; the composition comprises a polymeric carrier, and wherein the polymeric carrier comprises a biodegradable polymer; the composition comprises a polymeric carrier, and wherein the polymeric carrier comprises a non-biodegradable polymer; the composition comprises a polymeric carrier, and wherein the polymeric carrier comprises a hydrophilic polymer; the composition comprises a polymeric carrier, and wherein the polymeric carrier comprises a hydrophobic polymer; the composition comprises a polymeric carrier, and wherein the polymeric carrier comprises a polymer having hydrophilic domains; the composition comprises a polymeric carrier, and wherein the polymeric carrier comprises a polymer having hydrophobic domains; the composition comprises a polymeric carrier, and wherein the polymeric carrier comprises a non-conductive polymer; the composition comprises a polymeric carrier, and wherein the polymeric carrier comprises an elastomer; the composition comprises a polymeric carrier, and wherein the polymeric carrier comprises a hydrogel; the composition comprises a polymeric carrier, and wherein the polymeric carrier comprises a silicone polymer; the composition comprises a polymeric carrier, and wherein the polymeric carrier comprises a hydrocarbon polymer; the composition comprises a polymeric carrier, and wherein the polymeric carrier comprises a styrene-derived polymer; the composition comprises a polymeric carrier, and wherein the polymeric carrier comprises a butadiene polymer; the composition comprises a polymeric carrier, and wherein the polymeric carrier comprises a macromer; the composition comprises a polymeric carrier, and wherein the polymeric carrier comprises a poly(ethylene glycol) polymer; the composition comprises a polymeric carrier, and wherein the polymeric carrier comprises an amorphous polymer; the medical device comprises a lubricious coating; the anti-scarring agent is located within pores or holes of the medical device; the anti-scarring agent is located within a channel, lumen, or divet of the medical device; the medical device further comprises a second pharmaceutically active agent; the medical device further comprises an anti-inflammatory agent; the medical device further comprises an agent that inhibits infection; the medical device further comprises an agent that inhibits infection, and wherein the agent is an anthracycline; the medical device further comprises an agent that inhibits infection, and wherein the agent is doxorubicin; the medical device further comprises an agent that inhibits infection, and wherein the agent is mitoxantrone; the medical device further comprises an agent that inhibits infection, and wherein the agent is a fluoropyrimidine; the medical device further comprises an agent that inhibits infection, and wherein the agent is 5-fluorouracil (5-FU); the medical device further comprises an agent that inhibits infection, and wherein the agent is a folic acid antagonist; the medical device further comprises an agent that inhibits infection, and wherein the agent is methotrexate; the medical device further comprises an agent that inhibits infection, and wherein the agent is a podophylotoxin; the medical device further comprises an agent that inhibits infection, and wherein the agent is etoposide; the medical device further comprises an agent that inhibits infection, and wherein the agent is a camptothecin; the medical device further comprises an agent that inhibits infection, and wherein the agent is a hydroxyurea; the medical device further comprises an agent that inhibits infection, and wherein the agent is a platinum complex; the medical device further comprises an agent that inhibits infection, and wherein the agent is cisplatin; the medical device further comprises an anti-thrombotic agent; the medical device further comprises a visualization agent; the medical device further comprises a visualization agent, wherein the visualization agent is a radiopaque material, and wherein the radiopaque material further comprises a metal, a halogenated compound, or a barium containing compound; the medical device further comprises a visualization agent, wherein the visualization agent is a radiopaque material, and wherein the radiopaque material further comprises barium, tantalum, or technetium; the medical device further comprises a visualization agent, and wherein the visualization agent is a MRI responsive material; the medical device further comprises a visualization agent, and wherein the visualization agent further comprises a gadolinium chelate; the medical device further comprises a visualization agent, and wherein the visualization agent further comprises iron, magnesium, manganese, copper, or chromium; the medical device further comprises a visualization agent, and wherein the visualization agent further comprises an iron oxide compound; the medical device further comprises a visualization agent, and wherein the visualization agent further comprises a dye, pigment, or colorant; the medical device further comprises an echogenic material; the medical device further comprises an echogenic material, and wherein the echogenic material is in the form of a coating; the medical device is sterile; the anti-scarring agent is released into

tissue in the vicinity of the medical device after deployment of the medical device; the anti-scarring agent is released into tissue in the vicinity of the medical device after deployment of the medical device, and wherein the tissue is connective tissue; the anti-scarring agent is released into tissue in the vicinity of the medical device after deployment of the medical device, and wherein the tissue is muscle tissue; the anti-scarring agent is released into tissue in the vicinity of the medical device after deployment of the medical device, and wherein the tissue is nerve tissue; the anti-scarring agent is released into tissue in the vicinity of the medical device after deployment of the medical device, and wherein the tissue is epithelium tissue; the anti-scarring agent is released in effective concentrations from the medical device over a period ranging from the time of deployment of the medical device to about 1 year; the anti-scarring agent is released in effective concentrations from the medical device over a period ranging from about 1 month to 6 months; the anti-scarring agent is released in effective concentrations from the medical device over a period ranging from about 1-90 days; the anti-scarring agent is released in effective concentrations from the medical device at a constant rate; the anti-scarring agent is released in effective concentrations from the medical device at an increasing rate; the anti-scarring agent is released in effective concentrations from the medical device at a decreasing rate; the anti-scarring agent is released in effective concentrations from the composition comprising the anti-scarring agent by diffusion over a period ranging from the time of deployment of the medical device to about 90 days; the anti-scarring agent is released in effective concentrations from the composition comprising the anti-scarring agent by erosion of the composition over a period ranging from the time of deployment of the medical device to about 90 days; the medical device comprises about 0.01 μg to about 10 μg of the anti-scarring agent; the medical device comprises about 10 μg to about 10 mg of the anti-scarring agent; the medical device comprises about 10 mg to about 250 mg of the anti-scarring agent; the medical device comprises about 250 mg to about 1000 mg of the anti-scarring agent; the medical device comprises about 1000 mg to about 2500 mg of the anti-scarring agent; a surface of the medical device comprises less than 0.01 μg of the anti-scarring agent per mm^2 of medical device surface to which the anti-scarring agent is applied; a surface of the medical device comprises about 0.01 μg to about 1 μg of the anti-scarring agent per mm^2 of medical device surface to which the anti-scarring agent is applied; a surface of the medical device comprises about 1 μg to about 10 μg of the anti-scarring agent per mm^2 of medical device surface to which the anti-scarring agent is applied; a surface of the medical device comprises about 10 μg to about 250 μg of the anti-scarring agent per mm^2 of medical device surface to which the anti-scarring agent is applied; a surface of the medical device comprises about 250 μg to about 1000 μg of the anti-scarring agent of anti-scarring agent per mm^2 of medical device surface to which the anti-scarring agent is applied; a surface of the medical device comprises about 1000 μg to about 2500 μg of the anti-scarring agent per mm^2 of medical device surface to which the anti-scarring agent is applied; the combining is performed by direct affixing the agent or the composition to the electrical device; the combining is performed by spraying the agent or the component onto the electrical device; the combining is performed by electrospraying the agent or the composition onto the electrical device; the combining is performed by dipping the electrical device into a solution comprising the agent or the composition; the combining is performed by covalently attaching the agent or the composition to the electrical device; the combining is performed by non-covalently attaching the agent or the composition to the electrical device; the combining is performed by coating the electrical device with a substance that contains the agent or the composition; the combining is performed by coating the electrical device with a substance that absorbs the agent; the combining is performed by interweaving the electrical device with a thread composed of, or coated with, the agent or the composition; the combining is performed by completely covering the electrical device with a sleeve that contains the agent or the composition; the combining is performed by covering a portion of the electrical device with a sleeve that contains the agent or the composition; the combining is performed by completely covering the electrical device with a cover that contains the agent or the composition; the combining is performed by covering a portion of the electrical device with a cover that contains the agent or the composition; the combining is performed by completely covering the electrical device with an electrospun fabric that contains the agent or the composition; the combining is performed by covering a portion of the electrical device with an electrospun fabric that contains the agent or the composition; the combining is performed by completely covering the electrical device with a mesh that contains the agent or the composition; the combining is performed by covering a portion of the electrical device with a mesh that contains the agent or the composition; the combining is performed by constructing a portion of the electrical device with the agent or the composition; the combining is performed by impregnating the electrical device with the agent or the composition; the combining is performed by constructing a portion of the electrical device from a degradable polymer that releases the agent; the combining is performed by dipping the electrical device into a solution that comprise the agent and an inert solvent for the electrical device; the combining is performed by dipping the electrical device into a solution that comprises the agent and a solvent that will swill the electrical device; the combining is performed by dipping the electrical device into a solution that comprises the agent and a solvent that will dissolve the electrical device; the combining is performed by dipping the electrical device into a solution that comprises the agent, a polymer and an inert solvent for the electrical device; the combining is performed by dipping the electrical device into a solution that comprises the agent, a polymer and a solvent that will swill the electrical device; the combining is performed by dipping the electrical device into a solution that comprises the agent, a polymer and a solvent that will dissolve the electrical device; the combining is performed by spraying the electrical device into a solution that comprises the agent and an inert solvent for the electrical device; the combining is performed by spraying the electrical device into a solution that comprises the agent and a solvent that will swill the electrical device; the combining is performed by spraying the electrical device into a solution that comprises the agent and a solvent that will dissolve the electrical device; the combining is performed by spraying the electrical device into a solution that comprises the agent, a polymer and an inert solvent for the electrical device; the combining is performed by spraying the electrical device into a solution

that comprises the agent, a polymer and a solvent that will swill the electrical device; and the combining is performed by spraying the electrical device into a solution that comprises the agent, a polymer and a solvent that will dissolve the electrical device.

[1071] The following examples are offered by way of illustration, and not by way of limitation.

EXAMPLES

Example 1

Parylene Coating

[1072] A metallic portion of an electrical device (e.g., a neurostimulator or an electrical lead) is washed by dipping it into HPLC grade isopropanol. A parylene primer layer (about 1 to 10 um) is deposited onto the cleaned electrical device using a parylene coater (e.g., PDS 2010 LABCOATER 2 from Cookson Electronics) and di-p-xylylene (PARYLENE N) or dichloro-di-p-xylylene (PARYLENE D) (both available from Specialty Coating Systems, Indianapolis, Ind.) as the coating feed material.

Example 2

Paclitaxel Coating—Partial Coating

[1073] Paclitaxel solutions are prepared by dissolving paclitaxel (5 mg, 10 mg, 50 mg, 100 mg, 200 mg and 500 mg) in 5 ml HPLC grade THF. A coated portion of a parylene-coated device (as prepared in, e.g., Example 1) is dipped into a paclitaxel/THF solution. After a selected incubation time, the device is removed from the solution and dried in a forced air oven (50° C.). The device then is further dried in a vacuum oven overnight. The amount of paclitaxel used in each solution and the incubation time is varied such that the amount of paclitaxel coated onto the device is in the range of 0.06 $\mu g/mm^2$ to 10 $\mu g/mm^2$ (μg paclitaxel/mm^2 of the device which is coated with paclitaxel after being placed in the THF/paclitaxel solution). The time during which the device is maintained in the paclitaxel/THF solution may be varied, where longer soak times generally provide for more paclitaxel to be adsorbed onto the device. In additional examples, one of the following exemplary compounds may be used in lieu of paclitaxel: mitoxantrone, doxorubicin, epithilone B, etoposide, TAXOTERE, tubercidin, vinblastine, geldanamycin, simvastatin, sirolimus, everolimus, halifuginone, mycophenolic acid, 1-alpha-25 dihydroxy vitamin D_3, Bay 11-7082, SB202190, mithramycin, pimecrolimus and sulconizole.

Example 3

Paclitaxel Coating—Complete Coating

[1074] Paclitaxel solutions are prepared by dissolving paclitaxel (5 mg, 10 mg, 50 mg, 100 mg, 200 mg and 500 mg) in 5 ml HPLC grade THF. An entire parylene coated device (coated as in, e.g., Example 1) is then dipped into the paclitaxel/THF solution. After a selected incubation time, the device is removed and dried in a forced air oven (50° C.). The device is then further dried in a vacuum oven overnight. The amount of paclitaxel used in each solution and the incubation time is varied such that the amount of paclitaxel coated onto the device is in the range of 0.06 $\mu g/mm^2$ to 10 $\mu g/mm^2$. In additional examples, one of the following exemplary compounds may be used in lieu of paclitaxel: mitoxantrone, doxorubicin, epithilone B, etoposide, TAXOTERE, tubercidin, halifuginone, vinblastine, geldanamycin, simvastatin, sirolimus, everolimus, pimecrolimus, mycophenolic acid, 1-alpha-25 dihydroxy vitamin D_3, Bay 11-7082, SB202190, mithramycin and sulconizole.

Example 4

Application of a Parylene Overcoat

[1075] A paclitaxel coated device (prepared as in, e.g., Example 2 or 3) is placed in a parylene coater and an additional thin layer of parylene is deposited on the paclitaxel coated device using the procedure described in Example 1. The coating duration is selected to provide a parylene top-coat thickness that will cause the device to have a desired elution profile for the paclitaxel.

Example 5

Application of an Echogenic Coating Layer

[1076] DESMODUR (an isocyanate pre-polymer Bayer AG) (25% w/v) is dissolved in a 50:50 mixture of dimethylsulfoxide and tetrahydrofuran. A paclitaxel/parylene overcoated device (prepared as in, e.g., Example 4) is then dipped into the pre-polymer solution. The device is removed from the solution after a selected incubation time, and the coating is then partially dried at room temperature for 3 to 5 minutes. The device is then immersed in a beaker of water (room temperature) for 3-5 minutes to cause the polymerization reaction to occur rapidly. An echogenic coating is formed.

Example 6

Paclitaxel/Polymer Coating—Partial Coating

[1077] Several 5% solutions of poly(ethylene-co-vinyl acetate) {EVA} (60% vinyl acetate) are prepared using THF as the solvent. Selected amounts of paclitaxel (0.01%, 0.05%, 0.1%, 0.5%, 1%, 5%, 10%, 20%, 30% (w/w drug to polymer) are added to the EVA solutions. An electrical device or a portion thereof is dipped into a paclitaxel/EVA solution. After removing the device from the solution, the coating is dried by placing the device in a forced air oven (40° C.) for 3 hours. The coated device is then further dried under vacuum for 24 hours. This dip coating process may be repeated to increase the amount of polymer/paclitaxel coated onto the device. In addition, higher paclitaxel concentrations in the polymer/THF/paclitaxel solution and/or a longer soak time may be used to increase the amount of polymer/paclitaxel that is coated onto the device. In additional examples, one of the following exemplary compounds may be used in lieu of paclitaxel: mitoxantrone, mithramycin, doxorubicin, epithilone B, etoposide, TAXOTERE, tubercidin, vinblastine, geldanamycin, Simvastatin, halifuginone, sirolimus, everolimus, pimecrolimus, mycophenolic acid, 1-alpha-25 dihydroxy vitamin D3, Bay 11-7082, SB202190, and sulconizole.

Example 7

Paclitaxel-Heparin Coating

[1078] Several 5% solutions of poly(ethylene-co-vinyl acetate) {EVA} (60% vinyl acetate) are prepared using THF

as the solvent. Selected amounts (0.01%, 0.05%, 0.1%, 0.5%, 1%, 5%, 10%, 20%, 30% (w/w drug to polymer) of paclitaxel and a solution of tridodecyl methyl ammonium chloride-heparin complex (PolySciences) are added to each of the EVA solutions. All or a portion of an electrical device is dipped into the paclitaxel/EVA solution. After removing the device from the solution, the coating is dried by placing the device in a forced air oven (40° C.) for 3 hours. The coated device is then further dried under vacuum for 24 hours. The dip coating process may be repeated to increase the amount of polymer/heparin complex coated onto the device. In additional examples, one of the following exemplary compounds may be used in lieu of paclitaxel: mitoxantrone, mithramycin, doxorubicin, epithilone B, etoposide, TAXOTERE, tubercidin, halifuginone, vinblastine, geldanamycin, simvastatin, sirolimus, everolimus, pimecrolimus, mycophenolic acid, 1-alpha-25 dihydroxy vitamin D_3, Bay 11-7082, SB202190, and sulconizole.

Example 8

Paclitaxel—Heparin/Heparin Coating

[1079] An uncoated portion of a paclitaxel-heparin coated device (prepared as in, e.g., Example 7) is dipped into a 5% EVA/THF solution containing a selected amount of a tridodecyl methyl ammonium chloride-heparin complex solution (PolySciences) (0.1%, 0.5%, 1%, 2.5%, 5%, 10% (v/v)). After removing the device from the solution, the coating is dried by placing the device in a forced air oven (40° C.) for 3 hours. The coated device is then further dried under vacuum for 24 hours. This provides a device with a paclitaxel/heparin coating on one or more portions of the device and a heparin coating on one or more other parts of the device. In additional examples, one of the following exemplary compounds may be used in lieu of paclitaxel: mitoxantrone, mithramycin, doxorubicin, epithilone B, etoposide, TAXOTERE, tubercidin, vinblastine, geldanamycin, halifuginone, simvastatin, sirolimus, everolimus, pimecrolimus, mycophenolic acid, 1-alpha-25 dihydroxy vitamin D_3, Bay 11-7082, SB202190, and sulconizole.

Example 9

Paclitaxel/Polymer Coating—Partial Coating

[1080] Several 5% solutions of poly(styrene-co-isobutylene-styrene) (SIBS) are prepared using THF as the solvent. A selected amount of paclitaxel is added to each SIBS solution. One or more portions of a device are dipped into the paclitaxel/SIBS solution. After removing the device from the solution, the coating is dried by placing the device in a forced air oven (40° C.) for 3 hours. The coated device is then further dried under vacuum for 24 hours. The dip coating process may be repeated to increase the amount of polymer/paclitaxel coated onto the device. In addition, higher paclitaxel concentrations in the polymer/THF/paclitaxel solution and/or a longer soak time may be used to increase the amount of polymer/paclitaxel that is coated onto the device. In additional examples, one of the following exemplary compounds may be used in lieu of paclitaxel: mitoxantrone, doxorubicin, epithilone B, etoposide, TAXOTERE, tubercidin, vinblastine, geldanamycin, simvastatin, mithramycin, pimecrolimus, sirolimus, everolimus, mycophenolic acid, 1-alpha-25 dihydroxy vitamin D_3, Bay 11-7082, SB202190, and sulconizole.

Example 10

Paclitaxel/Polymer Coating—Echogenic Overcoat

[1081] A paclitaxel-coated electrical device prepared as in Example 9 is dipped into a DESMODUR solution (50% w/v) (50:50 mixture of dimethylsulfoxide and tetrahydrofuran). The device is then removed and the coating is partially dried at room temperature for 3 to 5 minutes. The device is then immersed in a beaker of water (room temperature) for 3-5 minutes to cause the polymerization reaction to occur rapidly. An echogenic coating is thereby formed. In additional examples, one of the following exemplary compounds may be used in lieu of paclitaxel: mitoxantrone, doxorubicin, epithilone B, mithramycin, etoposide, TAXOTERE, tubercidin, vinblastine, geldanamycin, simvastatin, sirolimus, everolimus, pimecrolimus, mycophenolic acid, 1-alpha-25 dihydroxy vitamin D_3, Bay 11-7082, SB202190, and sulconizole.

Example 11

Polymer/Echogenic Coating

[1082] A 5% solution of poly(styrene-co-isobutylene-styrene) (SIBS) is prepared using THF as the solvent. An electrical device is dipped into the SIBS solution. After a selected incubation time, the device is removed from the solution, and the coating is dried by placing the device in a forced air oven (40° C.) for 3 hours. The coated device is then further dried under vacuum for 24 hours.

[1083] A coated device is dipped into a DESMODUR solution (50:50 mixture of dimethylsulfoxide and tetrahydrofuran). The device is then removed and the coating is then partially dried at room temperature for 3 to 5 minutes. The device is then immersed in a beaker of water (room temperature) for 3-5 minutes to cause the polymerization reaction to occur rapidly. The device is dried under vacuum for 24 hours at room temperature. All or a portion of the coated device is immersed into a solution of paclitaxel (5% w/v in methanol). The device is removed and dried at 40° C. for 1 hour and then under vacuum for 24 hours.

[1084] The amount of paclitaxel absorbed by the polymeric coating can be altered by changing the paclitaxel concentration, the immersion time as well as the solvent composition of the paclitaxel solution. In additional examples, one of the following exemplary compounds may be used in lieu of paclitaxel: mitoxantrone, mithramycin, doxorubicin, epithilone B, etoposide, TAXOTERE, tubercidin, vinblastine, geldanamycin, halifuginone, simvastatin, sirolimus, everolimus, pimecrolimus, mycophenolic acid, 1-alpha-25 dihydroxy vitamin D_3, Bay 11-7082, SB202190, and sulconizole.

Example 12

Paclitaxel/Siloxane Coating—Partial Coating

[1085] An electrical device is coated with a silioxane layer by exposing the device to gaseous tetramethylcyclotetrasiloxane that is then polymerized by low energy plasma polymerization onto the device surface. The thickness of the siloxane layer can be increased by increasing the polymerization time. After polymerization, a portion of the coated device is then immersed into a paclitaxel/THF solution (5%

w/v) for a selected period of time to allow the paclitaxel to absorb into the siloxane coating. The device is then removed from the solution and is dried for 2 hours at 40° C. in a forced air oven. The device is then further dried under vacuum at room temperature for 24 hours. The amount of paclitaxel coated onto the device can be varied by altering the concentration of the paclitaxel/THF solution and by altering the immersion time of the device in the paclitaxel THF solution. In additional examples, one of the following exemplary compounds may be used in lieu of paclitaxel: mitoxantrone, mithramycin, doxorubicin, epithilone B, etoposide, TAXOTERE, tubercidin, vinblastine, geldanamycin, halifuginone, simvastatin, sirolimus, everolimus, pimecrolimus, mycophenolic acid, 1-alpha-25 dihydroxy vitamin D_3, Bay 11-7082, SB202190, and sulconizole.

Example 13

Spray-Coated Devices

[1086] Several 2% solutions of poly(styrene-co-isobutylene-styrene) (SIBS) (50 ml) are prepared using THF as the solvent. A selected amount of paclitaxel (0.01%, 0.05%, 0.1%, 0.5%, 1%, 2.5%, 5%, 10% and 20% (w/w with respect to the polymer)) is added to each solution. An electrical device is held with a pair of tweezers and is then spray coated with one of the paclitaxel/polymer solutions using an airbrush. The device is then air-dried. The device is then held in a new location using the tweezers and a second coat of a paclitaxel/polymer solution having the same concentration is applied to the device. The device is air-dried and is then dried under vacuum at room temperature overnight. The total amount of paclitaxel coated onto the device can be altered by changing the paclitaxel content in the solution as well as by increasing the number of coatings that are applied. In additional examples, one of the following exemplary compounds may be used in lieu of paclitaxel: mitoxantrone, mithramycin, doxorubicin, epithilone B, etoposide, TAXOTERE, tubercidin, vinblastine, geldanamycin, simvastatin, sirolimus, everolimus, pimecrolimus, mycophenolic acid, 1-alpha-25 dihydroxy vitamin D_3, Bay 11-7082, SB202190, and sulconizole.

Example 14

Drug Coated Device-Non-Degradable

[1087] An electrical device is attached to a rotating mandrel. A solution of paclitaxel (5% w/w) in a polyurethane (CHRONOFLEX 85A; CardioTech Biomaterials)/THF solution (2.5% w/v) is then sprayed onto all or a portion of the outer surface of the device. The solution is sprayed on at a rate that ensures that the device is not damaged or saturated with the sprayed solution. The device is allowed to air dry after which it is dried under vacuum for 24 hours. In additional examples, one of the following exemplary compounds may be used in lieu of paclitaxel: mitoxantrone, mithramycin, doxorubicin, epithilone B, etoposide, TAXOTERE, tubercidin, vinblastine, geldanamycin, simvastatin, sirolimus, everolimus, pimecrolimus, mycophenolic acid, 1-alpha-25 dihydroxy vitamin D_3, Bay 11-7082, SB202190, and sulconizole.

Example 15

Drug Coated Device—Degradable

[1088] An electrical device is attached to a rotating mandrel. A paclitaxel (5% w/w) in a PLGA/ethyl acetate solution (2.5% w/v) is then sprayed onto all or portion of the outer surface of the device. The solution is sprayed on at a rate that ensures that the device is not damaged or saturated with the sprayed solution. The device is allowed to air dry, after which it is dried under vacuum at room temperature for 24 hours. In additional examples, one of the following exemplary compounds may be used in lieu of paclitaxel: mitoxantrone, doxorubicin, epithilone B, etoposide, mithramycin, TAXOTERE, tubercidin, vinblastine, geldanamycin, simvastatin, sirolimus, everolimus, pimecrolimus, mycophenolic acid, 1-alpha-25 dihydroxy vitamin D_3, Bay 11-7082, SB202190, and sulconizole.

Example 16

Drug Coated Device—Degradable Overcoat

[1089] A drug-coated electrical device prepared as in Example 14 or Example 15 is attached to a rotating mandrel. A PLGA/ethyl acetate solution (2.5% w/v) is then sprayed onto all or a portion of the outer surface of the device, such that a coating is formed over the first drug containing coating. The solution is sprayed on at a rate that ensures that the device is not damaged or saturated with the sprayed solution. The device is allowed to air dry after which it is dried under vacuum at room temperature for 24 hours.

Example 17

Drug-Loaded Microsphere Formulation

[1090] Paclitaxel (10% w/w) is added to a solution of PLGA (50/50, Mw 54,000) in DCM (5% w/v). The solution is vortexed and then poured into a stirred (overhead stirrer with a 3 bladed TEFLON coated stirrer) aqueous PVA solution (approx. 89% hydrolysed, Mw≈13,000, 2% w/v). The solution is stirred for 6 hours after which the solution is centrifuged to sediment the microspheres. The microspheres are resuspended in water. The centrifugation—ishing process is repeated 4 times. The final microsphere solution is flash frozen in an acetone/dry-ice bath. The frozen solution is then freeze-dried to produce a fine powder. The size of the microspheres formed can be altered by changing the stirring speed and/or the PVA solution concentration. The freeze dried powder can be resuspended in PBS or saline and can be used for direct injection, as an incubation fluid or as an irrigation fluid. In additional examples, one of the following exemplary compounds may be used in lieu of paclitaxel: mitoxantrone, doxorubicin, epithilone B, mithramycin, etoposide, TAXOTERE, tubercidin, vinblastine, geldanamycin, simvastatin, sirolimus, everolimus, pimecrolimus, mycophenolic acid, 1-alpha-25 dihydroxy vitamin D_3, Bay 11-7082, SB202190, and sulconizole.

Example 18

Drug Coated Device (Exterior Coating)

[1091] All or a portion of an electrical device is dipped into a polyurethane (CHRONOFLEX 85A)/THF solution (2.5% w/v). The coated device is allowed to air dry for 10 seconds. The device is then rolled in powdered paclitaxel that has been spread thinly on a piece of release liner to provide a device coated with between 0.1 to 10 mg of paclitaxel. The rolling process is done in such a manner that the paclitaxel powder predominantly adheres to the exterior

side of the coated device. The device is air-dried for 1 hour followed by vacuum drying at room temperature for 24 hours. In additional examples, one of the following exemplary compounds may be used in lieu of paclitaxel: mitoxantrone, doxorubicin, epithilone B, etoposide, TAXOTERE, tubercidin, vinblastine, geldanamycin, simvastatin, mithramycin, sirolimus, everolimus, pimecrolimus, mycophenolic acid, 1-alpha-25 dihydroxy vitamin D_3, Bay 11-7082, SB202190, and sulconizole.

Example 19

Drug Coated Device (Exterior Coating) with a Heparin Coating

[1092] A drug-coated device prepared as in Example 18 is further coated with a heparin coating. A device prepared as in Example 18 is dipped into a solution of heparin-benzalkonium chloride complex (1.5% (w/v) in isopropanol, STS Biopolymers). The device is removed from the solution and air-dried for 1 hour followed by vacuum drying for 24 hours. This process coats both the interior and exterior surfaces of the device with heparin.

Example 20

Partial Drug Coating of a Device

[1093] An electrical device is attached to a rotating mandrel. A mask system is set up so that only a portion of the device surface is exposed. A solution of paclitaxel (5% w/w) in a polyurethane (CHRONOFLEX 85A)/THF solution (2.5% w/v) is then sprayed onto the exposed portion of the device. The solution is sprayed on at a rate that ensures that the device is not damaged or saturated with the sprayed solution. The device is allowed to air dry after which it is dried under vacuum at room temperature for 24 hours. In additional examples, one of the following exemplary compounds may be used in lieu of paclitaxel: mitoxantrone, doxorubicin, epithilone B, etoposide, TAXOTERE, tubercidin, vinblastine, geldanamycin, mithramycin, simvastatin, sirolimus, everolimus, pimecrolimus, mycophenolic acid, 1-alpha-25 dihydroxy vitamin D_3, Bay 11-7082, SB202190, and sulconizole.

Example 21

Drug—Dexamethasone Coated Device

[1094] An electrical device is coated as in Example 20. The mask is then rearranged so that a previously masked portion of the device is exposed. The exposed portion of the device is then sprayed with a dexamethasone (10% w/w)/polyurethane (CHRONOFLEX 85A)/THF solution (2.5% w/v). The device is air dried, after which it is dried under vacuum at room temperature for 24 hours. In additional examples, one of the following exemplary compounds may be used in lieu of paclitaxel: mitoxantrone, doxorubicin, epithilone B, etoposide, TAXOTERE, tubercidin, vinblastine, mithramycin, geldanamycin, simvastatin, sirolimus, everolimus, pimecrolimus, mycophenolic acid, 1-alpha-25 dihydroxy vitamin D_3, Bay 11-7082, SB202190, and sulconizole.

Example 22

Drug—Heparin Coated Device

[1095] An electrical device is coated as in Example 20. The mask is then rearranged so that only a previously masked portion of the device is exposed. The exposed surface of the device is then sprayed with a heparin-benzalkonium chloride complex (1.5% (w/v) in isopropanol (STS Biopolymers). The sample is air dried after which it is dried under vacuum for 24 hours. In additional examples, one of the following exemplary compounds may be used in lieu of paclitaxel: mitoxantrone, doxorubicin, mithramycin, epithilone B, etoposide, TAXOTERE, tubercidin, vinblastine, geldanamycin, simvastatin, sirolimus, everolimus, pimecrolimus, mycophenolic acid, 1-alpha-25 dihydroxy vitamin D_3, Bay 11-7082, SB202190, and sulconizole.

Example 23

Drug-Dexamethaxone Coated Device

[1096] An electrical device is attached to a rotating mandrel. A solution of paclitaxel (5% w/w) and dexamethazone (5% w/w) in a PLGA (50/50, Mw 54,000)/ethyl acetate solution (2.5% w/v) is sprayed onto all or a portion of the device. The solution is sprayed on at a rate that ensures that the device is not damaged or saturated with the sprayed solution. The device is allowed to air dry after which it is dried under vacuum at room temperature for 24 hours. In additional examples, one of the following exemplary compounds may be used in lieu of paclitaxel: mitoxantrone, doxorubicin, mithramycin, epithilone B, etoposide, TAXOTERE, tubercidin, vinblastine, geldanamycin, simvastatin, sirolimus, everolimus, pimecrolimus, mycophenolic acid, 1-alpha-25 dihydroxy vitamin D_3, Bay 11-7082, SB202190, and sulconizole.

Example 24

Drug-Dexamethasone Coated Device (Sequential Coating)

[1097] An electrical device is attached to a rotating mandrel. A solution of paclitaxel (5% w/w) in a PLGA (50/50, Mw 54,000)/ethyl acetate solution (2.5% w/v) is sprayed onto the outer surface of the device. The solution is sprayed on at a rate that ensures that the device is not damaged or saturated with the sprayed solution. The device is allowed to air dry. A methanol solution of dexamethasone (2% w/v) is then sprayed onto the outer surface of the device (at a rate that ensures that the device is not damaged or saturated with the sprayed solution). The device is allowed to air dry, after which it is dried under vacuum at room temperature for 24 hours. In additional examples, one of the following exemplary compounds may be used in lieu of paclitaxel: mitoxantrone, doxorubicin, mithramycin, epithilone B, etoposide, TAXOTERE, tubercidin, vinblastine, geldanamycin, simvastatin, sirolimus, everolimus, pimecrolimus, mycophenolic acid, 1-alpha-25 dihydroxy vitamin D_3, Bay 11-7082, SB202190, and sulconizole.

Example 25

Drug-Loading an Electrical Lead Comprising a Porous Electrode—Paclitaxel

[1098] 10 ml solutions of paclitaxel are prepared by weighing in 1 mg, 5 mg, 10 mg, 20 mg, 50 mg, 75 mg, 100 mg, 200 mg, and 500 mg paclitaxel into a 20 ml glass scintillation vial respectively and then adding HPLC grade acetone. The solutions are gently shaken on an orbital shaker

for 1 hour at room temperature. An electrical pacing lead that comprises a porous ball shaped electrode tip (Medtronic, Inc.) is placed on a bench and a glass microscope slide is placed under the tip portion of the lead. Using a 200 μl pipettor (Gilson) with the pipette tip touching the electode tip, the 0.1 mg/ml paclitaxel solution is slowly applied to the porous electrode tip until the electrode tip does not absorb any more solution. The electrode is then allowed to air dry for 6 hours. The process is repeated for all the prepared paclitaxel solutions on a fresh electrode.

Example 26

Drug-Loading an Electrical Lead Comprising a Porous Electrode—Paclitaxel/Beclomethasone

[1099] Several saturated 10 ml acetone solutions of beclomethasone diproprionate anhydrous are prepared by adding the beclomethasone diproprionate anhydrous to 10 ml acetone in 20 ml glass scintillation vials until no more beclomethasone diproprionate anhydrous will dissolve and solid beclomethasone diproprionate anhydrous remains at the bottom of the vial. To each of these saturated solutions, 1 mg, 5 mg, 10 mg, 20 mg, 50 mg, 75 mg, 100 mg, 200 mg, and 500 mg paclitaxel are added respectively. The solutions are gently shaken on an orbital shaker for 1 hour at room temperature. An electrical pacing lead that comprises a porous ball shaped electrode tip (Medtronic, Inc.) is placed on a bench and a glass microscope slide is placed under the tip portion of the lead. Using a 200 uL Gilson pipettor with the pipette tip touching the electode tip, the 0.1 mg/ml paclitaxel solution is slowly applied to the porous electrode tip until the electrode tip will not absorb any more solution. The electrode is then allowed to air dry for 6 hour. The process is repeated for all the prepared paclitaxel solutions using a fresh electrode for each solution.

Example 27

Drug-Loading an Electrical Lead Comprising a Porous Electrode—Paclitaxel/Polymer

[1100] 10 ml solutions of paclitaxel are prepared by weighing in 1 mg, 5 mg, 10 mg, 20 mg, 50 mg, 75 mg, 100 mg 200 mg and 500 mg paclitaxel into a 20 ml glass scintillation vial respectively and then adding HPLC grade tetrahydrofuran (THF). 1 g of a MePEG(2000)-PDLLA (60:40) diblock copolymer is added to each vial. The solutions are gently shaken on an orbital shaker for 6 hours at room temperature. An electrical pacing lead that comprises a porous ball shaped electrode tip (Medtronic, Inc.) is placed on a bench and a glass microscope slide is placed under the tip portion of the lead. Using a 200 uL Gilson pipettor with the pipette tip touching the electrode tip, the 0.1 mg/ml paclitaxel solution is slowly applied to the porous electrode tip until the electrode tip will not absorb any more solution. The electrode is then allowed to air dry for 6 hour. The process is repeated for all the prepared paclitaxel solutions using a fresh electrode for each solution.

Example 28

Drug-Loading an Electrical Lead Comprising a Porous Electrode—Paclitaxel/Beclomethasone/Polymer

[1101] Several saturated 10 ml acetone solutions of beclomethasone diproprionate anhydrous are prepared by adding the beclomethasone diproprionate anhydrous to 10 ml acetone in 20 ml glass scintillation vials until no more beclomethasone diproprionate anhydrous will dissolve and solid beclomethasone diproprionate anhydrous remains at the bottom of the vial. To each of these saturated solutions, 1 mg, 5 mg, 10 mg, 20 mg, 50 mg, 75 mg, 100 mg, 200 mg, and 500 mg paclitaxel are added respectively. 1 g of a MePEG(2000)-PDLLA (60:40) diblock copolymer is added to each vial. The solutions are gently shaken on an orbital shaker for 6 hours at room temperature. An electrical pacing lead that comprises a porous ball shaped electrode tip (Medtronic) is placed on a bench and a glass microscope slide is placed under the tip portion of the lead. Using a 200 uL Gilson pipettor with the pipette tip touching the electode tip, the 0.1 mg/ml paclitaxel solution is slowly applied to the porous electrode tip until the electrode tip will not absorb any more solution. The electrode is then allowed to air dry for 6 hour. The process is repeated for all the prepared paclitaxel solutions using a fresh electrode for each solution.

Example 29

Drug-Loading an Electrical Lead Comprising a Porous Electrode—Paclitaxel Dipping

[1102] 10 ml solutions of paclitaxel are prepared by weighing in 1 mg, 5 mg, 10 mg, 20 mg, 50 mg, 75 mg, 100 mg, 200 mg, and 500 mg paclitaxel into a 20 ml glass scintillation vial respectively and then adding HPLC grade acetone. The solutions are gently shaken on an orbital shaker for 1 hour at room temperature. The tip of an electrical pacing lead that comprises a porous ball shaped electrode tip (Medtronic, Inc.) is immersed to a depth of about 1 cm into the 0.1 mg/ml solution. After about 2 hours, the tip portion is removed from the solution and is allowed to air dry for 6 hour. The electrode is further dried under vacuum for 24 hours. The process is repeated for all the prepared paclitaxel solutions using a fresh electrode for each solution.

Example 30

Drug-Loading an Electrical Lead Comprising a Porous Electrode—Paclitaxel/Beclomethasone

[1103] Several saturated 10 ml acetone solutions of beclomethasone diproprionate anhydrous are prepared by adding the beclomethasone diproprionate anhydrous to 10 ml acetone in 20 ml glass scintillation vials until no more beclomethasone diproprionate anhydrous will dissolve and solid beclomethasone diproprionate anhydrous remains at the bottom of the vial. To each of these saturated solutions, 1 mg, 5 mg, 10 mg, 20 mg, 50 mg, 75 mg, 100 mg, 200 mg, and 500 mg paclitaxel are added respectively. The solutions are gently shaken on an orbital shaker for 1 hour at room temperature. The tip of an electrical pacing lead that comprises a porous ball shaped electrode tip (Medtronic) is immersed to a depth of about 1 cm into the 0.1 mg/ml solution. After about 2 hours, the tip portion is removed from the solution and is allowed to air dry for 6 hour. The electrode is further dried under vacuum for 24 hours. The process is repeated for all the prepared paclitaxel solutions using a fresh electrode for each solution.

Example 31

Drug-Loading a Screw-in Electrical Lead—Paclitaxel Dipping

[1104] 10 ml solutions of paclitaxel are prepared by weighing in 1 mg, 5 mg, 10 mg, 20 mg, 50 mg, 75 mg, 100

mg, 200 mg, and 500 mg paclitaxel into a 20 ml glass scintillation vial respectively and then adding HPLC grade methanol. The solutions are gently shaken on an orbital shaker for 1 hour at room temperature. The tip of an electrical pacing lead that comprises a screw in electrode tip (e.g., CAPSUREFIX NOVUS 5076, Medtronic, Inc.) is immersed to a depth of about 1 cm into the 0.1 mg/ml solution. After about 2 hours, the tip portion is removed from the solution and is allowed to air dry for 6 hour. The electrode is further dried under vacuum for 24 hours. The process is repeated for all the prepared paclitaxel solutions using a fresh electrode for each solution.

Example 32

Drug-Loading a Screw-in Electrical Lead—Paclitaxel Dipping

[1105] 10 ml solutions of paclitaxel are prepared by weighing in 1 mg, 5 mg, 10 mg, 20 mg, 50 mg, 75 mg, 100 mg, 200 mg, and 500 mg paclitaxel into a 20 ml glass scintillation vial respectively and then adding HPLC grade methanol. The solutions are gently shaken on an orbital shaker for 1 hour at room temperature. The tip of an electrical pacing lead that comprises a screw in electrode tip (e.g., CAPSUREFIX NOVUS 5076) is immersed to a depth of about 1 cm into the 0.1 mg/ml solution. After about 2 hours, the tip portion is removed from the solution and is allowed to air dry for 6 hour. The electrode is further dried under vacuum for 24 hours. The process is repeated for all the prepared paclitaxel solutions using a fresh electrode for each solution.

Example 33

Drug-Loading a Screw-in Electrical Lead—Paclitaxel/Polymer Dipping

[1106] A polyurethane solution (CHRONOFLEX AL 85 A) is prepared by dissolving 20 g of the polyurethane in 200 ml tetrahydrofuran (THF). 10 ml aliquots of this solution are placed in 20 ml glass scintillation vials. 1 mg, 5 mg, 10 mg, 20 mg, 50 mg, 75 mg, 100 mg, 200 mg, and 500 mg paclitaxel are then added to each of the vials respectively. The solutions are tumbled for 3 hours at 20 rpm. The tip of an electrical pacing lead that comprises a screw in electrode tip (e.g., CAPSUREFIX NOVUS 5076) is immersed to a depth of about 1 cm into the 0.1 mg/ml paclitaxel solution and then it is slowly withdrawn from the solution. The coated portion is allowed to air dry for 10 min. The screw-in portion of the electrode is then immersed in a solution of HPLC grade THF. After 1 hour the screw-in portion of the electrode is removed from the THF solution and is immersed in a fresh THF solution for 30 min. The electrode is then removed from the THF solution and is allowed to air dry for 2 hour. The electrode is further dried under vacuum for 24 hours. The process is repeated for all the prepared paclitaxel solutions using a fresh electrode for each solution.

Example 34

Drug-Loading a Screw-in Electrical Lead—Halofuginone/Polymer Spraying

[1107] A polyurethane solution (CHRONOFLEX AL 85 A) is prepared by dissolving 20 g of the polyurethane in 200 ml tetrahydrofuran (THF). 10 ml aliquots of this solution are placed in 20 ml glass scintillation vials. 1 mg, 5 mg, 10 mg, 20 mg, 50 mg, 75 mg, 100 mg, 200 mg, and 500 mg halofuginone are then added to each of the vials respectively. The solutions are tumbled for 3 hours at 20 rpm. The tip of an electrical pacing lead that comprises a screw in electrode tip (e.g., CAPSUREFIX NOVUS 5076) is screwed into the end of a silastic rod until the screw-in portion is completely incorporated into the silastic rod. The silastic rod it the attached to an overhead stirrer and the stir speed is set at 40 rpm. The 0.1 mg/ml halofuginone solution is placed in a 3 ml glass syringe that is then attached to an ultrasonic spray head (Sonus, Inc). The syringe is placed in a syringe pump. The solution is then sprayed onto the tip portion of the lead at a flow rate of 0.5 ml/min. Once the electrical lead tip is evenly coated with a halofuginone/polymer solution, the spraying is stopped and the coating is allowed to air dry for 1 hour. The electrode is unscrewed from the silastic rod. The electrode is further dried under vacuum for 24 hours. The process is repeated for all the prepared halofuginone solutions using a fresh electrode each time.

Example 35

Drug-Loading an Electrode Annular Shaped Monolithic Controlled Release Device—Paclitaxel

[1108] 10 ml solutions of paclitaxel are prepared by weighing in 1 mg, 5 mg, 10 mg, 20 mg, 50 mg, 75 mg, 100 mg, 200 mg, and 500 mg paclitaxel into a 20 ml glass scintillation vial respectively and then adding HPLC grade methanol. The solutions are gently shaken on an orbital shaker for 1 hour at room temperature. A silicone rubber annular shaped monolithic controlled release device used in the construction of a CAPSURE Z lead (Model 5534, Medtronic, Inc), is immersed in the 0.1 mg/ml paclitaxel solution for 3 hours. Using a pair of tweezers, the silicone rubber piece is removed from the solution, gently shaken to remove the excess solution and is then air dried for 5 hour. The air dried component is then dried under vacuum for 24 hours. The drug loaded silicone rubber component is then used in the assembly of the lead.

Example 36

Drug-Loading an Electrode Annular Shaped Monolithic Controlled Release Device—Paclitaxel/Dexamethasone

[1109] Several saturated 10 ml methanol solutions of dexamethasone are prepared by adding the dexamethasone to 10 ml methanol in 20 ml glass scintillation vials until no more dexamethasone will dissolve and solid dexamethasone remains at the bottom of the vial. To each of these saturated solutions, 1 mg, 5 mg, 10 mg, 20 mg, 50 mg, 75 mg, 100 mg, 200 mg, and 500 mg paclitaxel are added respectively. The solutions are gently shaken on an orbital shaker for 1 hour at room temperature. A silicone rubber annular shaped monolithic controlled release device used in the construction of a CAPSURE Z lead (Medtronic, Inc) is immersed in the 0.1 mg/ml paclitaxel solution for 3 hours. Using a pair of tweezers, the silicone rubber piece is removed from the solution, gently shaken to remove the excess solution and is then air dried for 5 hour. The air dried component is then dried under vacuum for 24 hours. The drug loaded silicone rubber component is then used in the assembly of the lead.

Example 37

Drug-Loading a Screw-in Electrical Lead—Rapamycin/Polymer Dip Coating

[1110] A polyurethane solution (CHRONOFLEX AL 85 A) is prepared by dissolving 20 g of the polyurethane in 200 ml tetrahydrofuran (THF). 10 ml aliquots of this solution are placed in 20 ml glass scintillation vials. 1 mg, 5 mg, 10 mg, 20 mg, 50 mg, 75 mg, 100 mg, 200 mg, and 500 mg rapamycin are then added to each of the vials respectively. The solutions are tumbled for 3 hours at 20 rpm. The tip of an electrical pacing lead that comprises a screw in electrode tip (e.g., CAPSUREFIX NOVUS 5076, Medtronic, Inc.) is screwed into the end of a silastic rod until the screw-in portion is completely incorporated into the silastic rod. The 0.1 mg/ml rapamycin solution is placed in a thin glass tube that is sealed at one end. The electrical lead is dipped into the solution and is then gradually withdrawn from the solution. The coated electrode is clamped such that the coated portion is suspended in the air. The coating is then air dried for 1 hour. The electrode is unscrewed from the silastic rod. The electrode is further dried under vacuum for 24 hours. The process is repeated for all the prepared rapamycin solutions using a fresh electrode each time.

Example 38

Screening Assay for Assessing the Effect of Various Compounds on Nitric Oxide Production by Macrophages

[1111] The murine macrophage cell line RAW 264.7 was trypsinized to remove cells from flasks and plated in individual wells of a 6-well plate. Approximately 2×10^6 cells were plated in 2 mL of media containing 5% heat-inactivated fetal bovine serum (FBS). RAW 264.7 cells were incubated at 37° C. for 1.5 hours to allow adherence to plastic. Mitoxantrone was prepared in DMSO at a concentration of 10^{-2} M and serially diluted 10-fold to give a range of stock concentrations (10^{-8} M to 10^{-2} M). Media was then removed and cells were incubated in 1 ng/mL of recombinant murine IFNγ and 5 ng/mL of LPS with or without mitoxantrone in fresh media containing 5% FBS. Mitoxantrone was added to cells by directly adding mitoxantrone DMSO stock solutions, prepared earlier, at a 1/1000 dilution, to each well. Plates containing IFNγ, LPS plus or minus mitoxantrone were incubated at 37° C. for 24 hours (*Chem. Ber.* (1879) 12: 426; *J. AOAC* (1977) 60-594; *Ann. Rev. Biochem.* (1994) 63:175).

[1112] At the end of the 24 hour period, supernatants were collected from the cells and assayed for the production of nitrites. Each sample was tested in triplicate by aliquoting 50 μl of supernatant in a 96-well plate and adding 50 μl of Greiss Reagent A (0.5 g sulfanilamide, 1.5 mL H_3PO_4, 48.5 mL ddH_2O) and 50 μl of Greiss Reagent B (0.05 g N-(1-naphthyl)-ethylenediamine, 1.5 mL H_3PO_4, 48.5 mL ddH_2O). Optical density was read immediately on microplate spectrophotometer at 562 nm absorbance. Absorbance over triplicate wells was averaged after subtracting background and concentration values were obtained from the nitrite standard curve (1 μM to 2 mM). Inhibitory concentration of 50% (IC_{50}) was determined by comparing average nitrite concentration to the positive control (cell stimulated with IFNγ and LPS). An average of n=4 replicate experiments was used to determine IC_{50} values for mitoxantrone (see, **FIG. 2** (IC_{50}=927 nM)). The IC_{50} values for the following additional compounds were determined using this assay: IC_{50} (nM): paclitaxel, 7; CNI-1493, 249; halofuginone, 12; geldanamycin, 51; anisomycin, 68; 17-AAG, 840; epirubicin hydrochloride, 769.

Example 39

Screening Assay for Assessing the Effect of Various Agents on TNF-Alpha Production by Macrophages

[1113] The human macrophage cell line, THP-1 was plated in a 12 well plate such that each well contains 1×10^6 cells in 2 mL of media containing 10% FCS. Opsonized zymosan was prepared by resuspending 20 mg of zymosan A in 2 mL of ddH_2O and homogenizing until a uniform suspension was obtained. Homogenized zymosan was pelleted at 250 g and resuspended in 4 mL of human serum for a final concentration of 5 mg/mL and incubated in a 37° C. water bath for 20 minutes to enable opsonization. Bay 11-7082 was prepared in DMSO at a concentration of 10^{-2} M and serially diluted 10-fold to give a range of stock concentrations (10^{-8} M to 10^{-2} M) (*J. Immunol.* (2000) 165: 411-418; *J. Immunol.* (2000) 164: 4804-4811; *J. Immunol Meth.* (2000) 235 (1-2): 33-40).

[1114] THP-1 cells were stimulated to produce TNFα by the addition of 1 mg/mL opsonized zymosan. Bay 11-7082 was added to THP-1 cells by directly adding DMSO stock solutions, prepared earlier, at a 1/1000 dilution, to each well. Each drug concentration was tested in triplicate wells. Plates were incubated at 37° C. for 24 hours.

[1115] After a 24 hour stimulation, supernatants were collected to quantify TNFα production. TNFα concentrations in the supernatants were determined by ELISA using recombinant human TNFα to obtain a standard curve. A 96-well MaxiSorb plate was coated with 100 μl of anti-human TNFα Capture Antibody diluted in Coating Buffer (0.1M sodium carbonate pH 9.5) overnight at 4° C. The dilution of Capture Antibody used was lot-specific and was determined empirically. Capture antibody was then aspirated and the plate washed 3 times with Wash Buffer (PBS, 0.05% TWEEN-20). Plates were blocked for 1 hour at room temperature with 200 μl/well of Assay Diluent (PBS, 10% FCS pH 7.0). After blocking, plates were washed 3 times with Wash Buffer. Standards and sample dilutions were prepared as follows: (a) sample supernatants were diluted 1/8 and 1/16; (b) recombinant human TNFα was prepared at 500 pg/mL and serially diluted to yield as standard curve of 7.8 pg/mL to 500 pg/mL. Sample supernatants and standards were assayed in triplicate and were incubated at room temperature for 2 hours after addition to the plate coated with Capture Antibody. The plates were washed 5 times and incubated with 100 μl of Working Detector (biotinylated anti-human TNFα detection antibody+avidin-HRP) for 1 hour at room temperature. Following this incubation, the plates were washed 7 times and 100 μl of Substrate Solution (tetramethylbenzidine, H_2O_2) was added to plates and incubated for 30 minutes at room temperature. Stop Solution (2 N H_2SO_4) was then added to the wells and a yellow color reaction was read at 450 nm with A correction at 570 nm. Mean absorbance was determined from triplicate data readings and the mean background was subtracted. TNFα concentration values were obtained from the standard curve.

Inhibitory concentration of 50% (IC_{50}) was determined by comparing average TNFα concentration to the positive control (THP-1 cells stimulated with opsonized zymosan). An average of n=4 replicate experiments was used to determine IC_{50} values for Bay 11-7082 (see **FIG. 3**; IC_{50}=810 nM)) and rapamycin (IC_{50}=51 nM; **FIG. 4**). The IC_{50} values for the following additional compounds were determined using this assay: IC_{50} (nM): geldanamycin, 14; mycophenolic acid, 756; mofetil, 792; chlorpromazine, 6; CNI-1493, 0.15; SKF 86002, 831; 15-deoxy prostaglandin J2, 742; fascaplysin, 701; podophyllotoxin, 75; mithramycin, 570; daunorubicin, 195; celastrol, 87; chromomycin A3, 394; vinorelbine, 605; vinblastine, 65.

Example 40

Surgical Adhesions Model to Assess Fibrosis Inhibiting Agents in Rats

[1116] The rat caecal sidewall model is used to as to assess the anti-fibrotic capacity of formulations in vivo. Sprague Dawley rats are anesthetized with halothane. Using aseptic precautions, the abdomen is opened via a midline incision. The caecum is exposed and lifted out of the abdominal cavity. Dorsal and ventral aspects of the caecum are successively scraped a total of 45 times over the terminal 1.5 cm using a #10 scalpel blade. Blade angle and pressure are controlled to produce punctate bleeding while avoiding severe tissue damage. The left side of the abdomen is retracted and everted to expose a section of the peritoneal wall that lies proximal to the caecum. The superficial layer of muscle (transverses abdominis) is excised over an area of 1×2 cm^2, leaving behind tom fibres from the second layer of muscle (internal oblique muscle). Abraded surfaces are tamponaded until bleeding stops. The abraded caecum is then positioned over the sidewall wound and attached by two sutures. The formulation is applied over both sides of the abraded caecum and over the abraded peritoneal sidewall. A further two sutures are placed to attach the caecum to the injured sidewall by a total of 4 sutures and the abdominal incision is closed in two layers. After 7 days, animals are evaluated post mortem with the extent and severity of adhesions being scored both quantitatively and qualitatively.

Example 41

Surgical Adhesions Model to Assess Fibrosis Inhibiting Agents in Rabbits

[1117] The rabbit uterine horn model is used to assess the anti-fibrotic capacity of formulations in vivo. Mature New Zealand White (NZW) female rabbits are placed under general anesthetic. Using aseptic precautions, the abdomen is opened in two layers at the midline to expose the uterus. Both uterine horns are lifted out of the abdominal cavity and assessed for size on the French Scale of catheters. Horns between #8 and #14 on the French Scale (2.5-4.5 mm diameter) are deemed suitable for this model. Both uterine horns and the opposing peritoneal wall are abraded with a #10 scalpel blade at a 45° angle over an area 2.5 cm in length and 0.4 cm in width until punctuate bleeding is observed. Abraded surfaces are tamponaded until bleeding stops. The individual horns are then opposed to the peritoneal wall and secured by two sutures placed 2 mm beyond the edges of the abraded area. The formulation is applied and the abdomen is closed in three layers. After 14 days, animals are evaluated post mortem with the extent and severity of adhesions being scored both quantitatively and qualitatively.

Example 42

Screening Assay for Assessing the Effect of Various Compounds on Cell Proliferation

[1118] Fibroblasts at 70-90% confluency were trypsinized, replated at 600 cells/well in media in 96-well plates and allowed to attach overnight. Mitoxantrone was prepared in DMSO at a concentration of 10^{-2} M and diluted 10-fold to give a range of stock concentrations (10^{-8} M to 10^{-2} M). Drug dilutions were diluted 1/1000 in media and added to cells to give a total volume of 200 μl/well. Each drug concentration was tested in triplicate wells. Plates containing fibroblasts and mitoxantrone were incubated at 37° C. for 72 hours (*In vitro toxicol.* (1990) 3: 219; *Biotech. Histochem.* (1993) 68: 29; *Anal. Biochem.* (1993) 213: 426).

[1119] To terminate the assay, the media was removed by gentle aspiration. A 1/400 dilution of CYQUANT 400×GR dye indicator (Molecular Probes; Eugene, Oreg.) was added to 1× Cell Lysis buffer, and 200 μl of the mixture was added to the wells of the plate. Plates were incubated at room temperature, protected from light for 3-5 minutes. Fluorescence was read in a fluorescence microplate reader at ~480 nm excitation wavelength and ~520 nm emission maxima. Inhibitory concentration of 50% (IC_{50}) was determined by taking the average of triplicate wells and comparing average relative fluorescence units to the DMSO control. An average of n=4 replicate experiments was used to determine IC_{50} values. The IC_{50} values for the following compounds were determined using this assay: IC_{50} (nM): mitoxantrone, 20 (**FIG. 5**); rapamycin, 19 (**FIG. 6**); paclitaxel, 23 (**FIG. 7**); mycophenolic acid, 550; mofetil, 601; GW8510, 98; simvastatin, 885; doxorubicin, 84; geldanamycin, 11; anisomycin, 435; 17-MG, 106; bleomycin, 86; halofuginone, 36; gemfibrozil, 164; ciprofibrate, 503; bezafibrate, 184; epirubicin hydrochloride, 57; topotemay, 81; fascaplysin, 854; tamoxifen, 13; etanidazole, 55; gemcitabine, 7; puromycin, 254; mithramycin, 156; daunorubicin, 51; L(−)-perillyl alcohol, 966; celastrol, 271; anacitabine, 225; oxalipatin, 380; chromomycin A3, 4; vinorelbine, 4; idarubicin, 34; nogalamycin, 5; 17-DMAG, 5; epothilone D, 2; vinblastine, 2; vincristine, 7; cytarabine, 137.

Example 43

Evaluation of Paclitaxel Containing Mesh on Intimal Hyperplasia Development in a Rat Balloon Injury Carotid Artery Model as an Example to Evaluate Fibrosis Inhibiting Agents

[1120] A rat balloon injury carotid artery model was used to demonstrate the efficacy of a paclitaxel containing mesh system on the development of intimal hyperplasia fourteen days following placement.

[1121] Control Group

[1122] Wistar rats weighing 400-500 g were anesthetized with 1.5% halothane in oxygen and the left external carotid artery was exposed. An A 2 French FOGARTY balloon embolectomy catheter (Baxter, Irvine, Calif.) was advanced through an arteriotomy in the external carotid artery down

the left common carotid artery to the aorta. The balloon was inflated with enough saline to generate slight resistance (approximately 0.02 ml) and it was withdrawn with a twisting motion to the carotid bifurcation. The balloon was then deflated and the procedure repeated twice more. This technique produced distension of the arterial wall and denudation of the endothelium. The external carotid artery was ligated after removal of the catheter. The right common carotid artery was not injured and was used as a control.

[1123] Local Perivascular Paclitaxel Treatment

[1124] Immediately after injury of the left common carotid artery, a 1 cm long distal segment of the artery was exposed and treated with a 1×1 cm paclitaxel-containing mesh (345 μg paclitaxel in a 50:50 PLG coating on a 10:90 PLG mesh). The wound was then closed the animals were kept for 14 days.

[1125] Histology and immunohistochemistry

[1126] At the time of sacrifice, the animals were euthanized with carbon dioxide and pressure perfused at 100 mmHg with 10% phosphate buffered formaldehyde for 15 minutes. Both carotid arteries were harvested and left overnight in fixative. The fixed arteries were processed and embedded in paraffin wax. Serial cross-sections were cut at 3 μm thickness every 2 mm within and outside the implant region of the injured left carotid artery and at corresponding levels in the control right carotid artery. Cross-sections were stained with Mayer's hematoxylin-and-eosin for cell count and with Movat's pentachrome stains for morphometry analysis and for extracellular matrix composition assessment.

[1127] Results

[1128] From **FIGS. 8-10**, it is evident that the perivascular delivery of paclitaxel using the paclitaxel mesh formulation resulted is a dramatic reduction in intimal hyperplasia.

Example 44

Effect of Paclitaxel and Other Anti-Microtubule Agents on Matrix Metalloproteinase Production

[1129] A. Materials and Methods

[1130] 1. IL-1Stimulated AP-1 Transcriptional Activity is Inhibited by Paclitaxel

[1131] Chondrocytes were transfected with constructs containing an AP-1 driven CAT reporter gene, and stimulated with IL-1, IL-1 (50 ng/ml) was added and incubated for 24 hours in the absence and presence of paclitaxel at various concentrations. Paclitaxel treatment decreased CAT activity in a concentration dependent manner (mean±SD). The data noted with an asterisk (*) have significance compared with IL-1-induced CAT activity according to a t-test, $P<0.05$. The results shown are representative of three independent experiments.

[1132] 2. Effect of Paclitaxel on IL-1 Induced AP-1 DNA Binding Activity, AP-1 DNA

[1133] Binding activity was assayed with a radiolabeled human AP-1 sequence probe and gel mobility shift assay. Extracts from chondrocytes untreated or treated with various amounts of paclitaxel (10^{-7} to 10^{-5} M) followed by IL-1β (20 ng/ml) were incubated with excess probe on ice for 30 minutes, followed by non-denaturing gel electrophoresis. The "corn" lane contains excess unlabeled AP-1 oligonucleotide. The results shown are representative of three independent experiments.

[1134] 3. Effect of Paclitaxel on IL-1 Induced MMP-1 and MMP-3 mRNA Expression

[1135] Cells were treated with paclitaxel at various concentrations (10^{-7} to 10^{-5} M) for 24 hours, then treated with IL-1β (20 ng/ml) for additional 18 hours in the presence of paclitaxel. Total RNA was isolated, and the MMP-1 mRNA levels were determined by Northern blot analysis. The blots were subsequently stripped and reprobed with ^{32}P-radiolabeled rat GAPDH cDNA, which was used as a housekeeping gene. The results shown are representative of four independent experiments. Quantitation of collagenase-1 and stromelysin-expression mRNA levels was conducted. The MMP-1 and MMP-3 expression levels were normalized with GAPDH.

[1136] 4. Effect of Other Anti-Microtubules on Collagenase Expression

[1137] Primary chondrocyte cultures were freshly isolated from calf cartilage. The cells were plated at 2.5×10^{6} per ml in 100×20 mm culture dishes and incubated in Ham's F12 medium containing 5% FBS overnight at 37° C. The cells were starved in serum-free medium overnight and then treated with anti-microtubule agents at various concentrations for 6 hours. IL-1 (20 ng/ml) was then added to each plate and the plates incubated for an additional 18 hours. Total RNA was isolated by the acidified guanidine isothiocyanate method and subjected to electrophoresis on a denatured gel. Denatured RNA samples (15 μg) were analyzed by gel electrophoresis in a 1% denatured gel, transferred to a nylon membrane and hydridized with the ^{32}P-labeled collagenase cDNA probe. ^{32}P-labeled glyceraldehyde phosphate dehydrase (GAPDH) cDNA as an internal standard to ensure roughly equal loading. The exposed films were scanned and quantitatively analyzed with IMAGEQUANT.

[1138] B. Results

[1139] 1. Promoters on the Family of Matrix Metalloproteinases

[1140] **FIG. 11A** shows that all matrix metalloproteinases contained the transcriptional elements AP-1 and PEA-3 with the exception of gelatinase B. It has been well established that expression of matrix metalloproteinases such as collagenases and stromelysins are dependent on the activation of the transcription factors AP-1. Thus inhibitors of AP-1 may inhibit the expression of matrix metalloproteinases.

[1141] 2. Effect of Paclitaxel on AP-1 Transcriptional Activity

[1142] As demonstrated in **FIG. 11B**, IL-1 stimulated AP-1 transcriptional activity 5-fold. Pretreatment of transiently transfected chondrocytes with paclitaxel reduced IL-1 induced AP-1 reporter gene CAT activity. Thus, IL-1 induced AP-1 activity was reduced in chondrocytes by paclitaxel in a concentration dependent manner (10^{-7} to 10^{-5} M). These data demonstrated that paclitaxel was a potent inhibitor of AP-1 activity in chondrocytes.

[1143] 3. Effect of Paclitaxel on AP-1 DNA Binding Activity

[1144] To confirm that paclitaxel inhibition of AP-1 activity was not due to nonspecific effects, the effect of paclitaxel on IL-1 induced AP-1 binding to oligonucleotides using chondrocyte nuclear lysates was examined. As shown in **FIG. 11C**, IL-1 induced binding activity decreased in lysates from chondrocyte which had been pretreated with paclitaxel at concentration 10^{-7} to 10^{-5} M for 24 hours. Paclitaxel inhibition of AP-1 transcriptional activity closely correlated with the decrease in AP-1 binding to DNA.

[1145] 4. Effect of Paclitaxel on Collagenase and Stromelysin Expression

[1146] Since paclitaxel was a potent inhibitor of AP-1 activity, the effect of paclitaxel or IL-1 induced collagenase and stromelysin expression, two important matrix metalloproteinases involved in inflammatory diseases was examined. Briefly, as shown in **FIG. 11D**, IL-1 induction increases collagenase and stromelysin mRNA levels in chondrocytes. Pretreatment of chondrocytes with paclitaxel for 24 hours significantly reduced the levels of collagenase and stromelysin mRNA. At 10^{-5} M paclitaxel, there was complete inhibition. The results show that paclitaxel completely inhibited the expression of two matrix metalloproteinases at concentrations similar to which it inhibits AP-1 activity.

[1147] 5. Effect of Other Anti-Microtubules on Collaqenase Expression

[1148] FIGS. **12**A-H demonstrate that anti-microtubule agents inhibited collagenase expression. Expression of collagenase was stimulated by the addition of IL-1 which is a proinflammatory cytokine. Pre-incubation of chondrocytes with various anti-microtubule agents, specifically LY290181, hexylene glycol, deuterium oxide, glycine ethyl ester, ethylene glycol bis-(succinimidylsuccinate), tubercidin, AlF_3, and epothilone, all prevented IL-1-induced collagenase expression at concentrations as low as 1×10^{-7} M.

[1149] 2. Discussion

[1150] Paclitaxel was capable of inhibiting collagenase and stromelysin expression in vitro at concentrations of 10^{-6} M. Since this inhibition may be explained by the inhibition of AP-1 activity, a required step in the induction of all matrix metalloproteinases with the exception of gelatinase B, it is expected that paclitaxel may inhibit other matrix metalloproteinases which are AP-1 dependent. The levels of these matrix metalloproteinases are elevated in all inflammatory diseases and play a principle role in matrix degradation, cellular migration and proliferation, and angiogenesis. Thus, paclitaxel inhibition of expression of matrix metalloproteinases such as collagenase and stromelysin can have a beneficial effect in inflammatory diseases.

[1151] In addition to paclitaxel's inhibitory effect on collagenase expression, LY290181, hexylene glycol, deuterium oxide, glycine ethyl ester, AlF_3, tubercidin epothilone, and ethylene glycol bis-(succinimidylsuccinate), all prevented IL-1-induced collagenase expression at concentrations as low as 1×10^{-7} M. Thus, anti-microtubule agents are capable of inhibiting the AP-1 pathway at varying concentrations.

Example 45

Inhibition of Angiogenesis by Paclitaxel

[1152] A. Chick Chorioallantoic Membrane ("CAM") Assays

[1153] Fertilized, domestic chick embryos were incubated for 3 days prior to shell-less culturing. In this procedure, the egg contents were emptied by removing the shell located around the air space. The interior shell membrane was then severed and the opposite end of the shell was perforated to allow the contents of the egg to gently slide out from the blunted end. The egg contents were emptied into round-bottom sterilized glass bowls and covered with petri dish covers. These were then placed into an incubator at 90% relative humidity and 3% CO_2 and incubated for 3 days.

[1154] Paclitaxel (Sigma, St. Louis, Mich.) was mixed at concentrations of 0.25, 0.5, 1, 5, 10, 30 μg per 10 μl aliquot of 0.5% aqueous methylcellulose. Since paclitaxel is insoluble in water, glass beads were used to produce fine particles. Ten microliter aliquots of this solution were dried on parafilm for 1 hour forming disks 2 mm in diameter. The dried disks containing paclitaxel were then carefully placed at the growing edge of each CAM at day 6 of incubation. Controls were obtained by placing paclitaxel-free methylcellulose disks on the CAMs over the same time course. After a 2° day exposure (day 8 of incubation) the vasculature was examined with the aid of a stereomicroscope. Liposyn II, a white opaque solution, was injected into the CAM to increase the visibility of the vascular details. The vasculature of unstained, living embryos were imaged using a Zeiss stereomicroscope which was interfaced with a video camera (Dage-MTI Inc., Michigan City, Ind.). These video signals were then displayed at 160× magnification and captured using an image analysis system (Vidas, Kontron; Etching, Germany). Image negatives were then made on a graphics recorder (Model 3000; Matrix Instruments, Orangeburg, N.Y.).

[1155] The membranes of the 8 day-old shell-less embryo were flooded with 2% glutaraldehyde in 0.1M sodium cacodylate buffer; additional fixative was injected under the CAM. After 10 minutes in situ, the CAM was removed and placed into fresh fixative for 2 hours at room temperature. The tissue was then washed overnight in cacodylate buffer containing 6% sucrose. The areas of interest were postfixed in 1% osmium tetroxide for 1.5 hours at 4° C. The tissues were then dehydrated in a graded series of ethanols, solvent exchanged with propylene oxide, and embedded in Spurr resin. Thin sections were cut with a diamond knife, placed on copper grids, stained, and examined in a Joel 1200EX electron microscope. Similarly, 0.5 mm sections were cut and stained with toluene blue for light microscopy.

[1156] At day 11 of development, chick embryos were used for the corrosion casting technique. Mercox resin (Ted Pella, Inc., Redding, Calif.) was injected into the CAM vasculature using a 30-gauge hypodermic needle. The casting material consisted of 2.5 grams of Mercox CL-2B polymer and 0.05 grams of catalyst (55% benzoyl peroxide) having a 5 minute polymerization time. After injection, the plastic was allowed to sit in situ for an hour at room temperature and then overnight in an oven at 65° C. The CAM was then placed in 50% aqueous solution of sodium hydroxide to digest all organic components. The plastic casts

were washed extensively in distilled water, air-dried, coated with gold/palladium, and viewed with the Philips 501B scanning electron microscope.

[1157] Results of the assay were as follows. At day 6 of incubation, the embryo was centrally positioned to a radially expanding network of blood vessels; the CAM developed adjacent to the embryo. These growing vessels lie close to the surface and are readily visible making this system an idealized model for the study of angiogenesis. Living, unstained capillary networks of the CAM may be imaged noninvasively with a stereomicroscope.

[1158] Transverse sections through the CAM show an outer ectoderm consisting of a double cell layer, a broader mesodermal layer containing capillaries which lie subjacent to the ectoderm, adventitial cells, and an inner, single endodermal cell layer. At the electron microscopic level, the typical structural details of the CAM capillaries are demonstrated. Typically, these vessels lie in close association with the inner cell layer of ectoderm.

[1159] After 48 hours exposure to paclitaxel at concentrations of 0.25, 0.5, 1, 5, 10, or 30 μg, each CAM was examined under living conditions with a stereomicroscope equipped with a video/computer interface in order to evaluate the effects on angiogenesis. This imaging setup was used at a magnification of 160× which permitted the direct visualization of blood cells within the capillaries; thereby blood flow in areas of interest may be easily assessed and recorded. For this study, the inhibition of angiogenesis was defined as an area of the CAM (measuring 2-6 mm in diameter) lacking a capillary network and vascular blood flow. Throughout the experiments, avascular zones were assessed on a 4 point avascular gradient (Table 1). This scale represents the degree of overall inhibition with maximal inhibition represented as a 3 on the avascular gradient scale. Paclitaxel was very consistent and induced a maximal avascular zone (6 mm in diameter or a 3 on the avascular gradient scale) within 48 hours depending on its concentration.

TABLE 1

AVASCULAR GRADIENT	
0	normal vascularity
1	lacking some microvascular movement
2*	small avascular zone approximately 2 mm in diameter
3*	avascularity extending beyond the disk (6 mm in diameter)

*indicates a positive antiangiogenesis response

[1160] The dose-dependent, experimental data of the effects of paclitaxel at different concentrations are shown in Table 2.

TABLE 2

Agent	Delivery Vehicle	Concentration	Inhibition/n
paclitaxel	methylcellulose (10 μl)	0.25 μg	2/11
	methylcellulose (10 μl)	0.5 μg	6/11
	methylcellulose (10 μl)	1 μg	6/15
	methylcellulose (10 μl)	5 μg	20/27
	methylcellulose (10 μl)	10 μg	16/21
	methylcellulose (10 μl)	30 μg	31/31

[1161] Typical paclitaxel-treated CAMs are also shown with the transparent methylcellulose disk centrally positioned over the avascular zone measuring 6 mm in diameter. At a slightly higher magnification, the periphery of such avascular zones is clearly evident; the surrounding functional vessels were often redirected away from the source of paclitaxel. Such angular redirecting of blood flow was never observed under normal conditions. Another feature of the effects of paclitaxel was the formation of blood islands within the avascular zone representing the aggregation of blood cells.

[1162] In summary, this study demonstrated that 48 hours after paclitaxel application to the CAM, angiogenesis was inhibited. The blood vessel inhibition formed an avascular zone which was represented by three transitional phases of paclitaxel's effect. The central, most affected area of the avascular zone contained disrupted capillaries with extravasated red blood cells; this indicated that intercellular junctions between endothelial cells were absent. The cells of the endoderm and ectoderm maintained their intercellular junctions and therefore these germ layers remained intact; however, they were slightly thickened. As the normal vascular area was approached, the blood vessels retained their junctional complexes and therefore also remained intact. At the periphery of the paclitaxel-treated zone, further blood vessel growth was inhibited which was evident by the typical redirecting or "elbowing" effect of the blood vessels.

Example 46

Screening Assay for Assessing the Effect of Paclitaxel on Smooth Muscle Cell Migration

[1163] Primary human smooth muscle cells were starved of serum in smooth muscle cell basal media containing insulin and human basic fibroblast growth factor (bFGF) for 16 hours prior to the assay. For the migration assay, cells were trypsinized to remove cells from flasks, washed with migration media and diluted to a concentration of $2\text{-}2.5\times10^5$ cells/mL in migration media. Migration media consists of phenol red free Dulbecco's Modified Eagle Medium (DMEM) containing 0.35% human serum albumin. A 100 μl volume of smooth muscle cells (approximately 20,000-25,000 cells) was added to the top of a Boyden chamber assembly (Chemicon QCM CHEMOTAXIS 96-well migration plate). To the bottom wells, the chemotactic agent, recombinant human platelet derived growth factor (rhPDGF-BB) was added at a concentration of 10 ng/mL in a total volume of 150 μl. Paclitaxel was prepared in DMSO at a concentration of 10^{-2} M and serially diluted 10-fold to give a range of stock concentrations (10^{-8} M to 10^{-2} M). Paclitaxel was added to cells by directly adding paclitaxel DMSO stock solutions, prepared earlier, at a 1/1000 dilution, to the cells in the top chamber. Plates were incubated for 4 hours to allow cell migration.

[1164] At the end of the 4 hour period, cells in the top chamber were discarded and the smooth muscle cells attached to the underside of the filter were detached for 30 minutes at 37° C. in Cell Detachment Solution (Chemicon). Dislodged cells were lysed in lysis buffer containing the DNA binding CYQUANT GR dye and incubated at room temperature for 15 minutes. Fluorescence was read in a fluorescence microplate reader at ~480 nm excitation wavelength and ~520 nm emission maxima. Relative fluores-

cence units from triplicate wells were averaged after subtracting background fluorescence (control chamber without chemoattractant) and average number of cells migrating was obtained from a standard curve of smooth muscle cells serially diluted from 25,000 cells/well down to 98 cells/well. Inhibitory concentration of 50% (IC_{50}) was determined by comparing the average number of cells migrating in the presence of paclitaxel to the positive control (smooth muscle cell chemotaxis in response to rhPDGF-BB). See **FIG. 13** (IC_{50}=0.76 nM). References: *Biotechniques* (2000) 29: 81; *J. Immunol Methods* (2001) 254: 85.

Example 47

Screening Assay for Assessing the Effect of Various Compounds on IL-1β Production by Macrophages

[**1165**] The human macrophage cell line, THP-1 was plated in a 12 well plate such that each well contains 1×10^6 cells in 2 mL of media containing 10% FCS. Opsonized zymosan was prepared by resuspending 20 mg of zymosan A in 2 mL of ddH_2O and homogenizing until a uniform suspension was obtained. Homogenized zymosan was pelleted at 250 g and resuspended in 4 mL of human serum for a final concentration of 5 mg/mL and incubated in a 37° C. water bath for 20 minutes to enable opsonization. Geldanamycin was prepared in DMSO at a concentration of 10^{-2} M and serially diluted 10-fold to give a range of stock concentrations (10^{-8} M to 10^{-2} M).

[**1166**] THP-1 cells were stimulated to produce IL-1β by the addition of 1 mg/mL opsonized zymosan. Geldanamycin was added to THP-1 cells by directly adding DMSO stock solutions, prepared earlier, at a 1/1000 dilution, to each well. Each drug concentration was tested in triplicate wells. Plates were incubated at 37° C. for 24 hours.

[**1167**] After a 24 hour stimulation, supernatants were collected to quantify IL-1β production. IL-1β concentrations in the supernatants were determined by ELISA using recombinant human IL-1β to obtain a standard curve. A 96-well MaxiSorb plate was coated with 100 μl of anti-human IL-1β Capture Antibody diluted in Coating Buffer (0.1M Sodium carbonate pH 9.5) overnight at 4° C. The dilution of Capture Antibody used was lot-specific and was determined empirically. Capture antibody was then aspirated and the plate washed 3 times with Wash Buffer (PBS, 0.05% TWEEN-20). Plates were blocked for 1 hour at room temperature with 200 μl/well of Assay Diluent (PBS, 10% FCS pH 7.0). After blocking, plates were washed 3 times with Wash Buffer. Standards and sample dilutions were prepared as follows: (a) sample supernatants were diluted 1/4 and 1/8; (b) recombinant human IL-1β was prepared at 1000 pg/mL and serially diluted to yield as standard curve of 15.6 pg/mL to 1000 pg/mL. Sample supernatants and standards were assayed in triplicate and were incubated at room temperature for 2 hours after addition to the plate coated with Capture Antibody. The plates were washed 5 times and incubated with 100 μl of Working Detector (biotinylated anti-human IL-1β detection antibody+avidin-HRP) for 1 hour at room temperature. Following this incubation, the plates were washed 7 times and 100 μl of Substrate Solution (Tetramethylbenzidine, H_2O_2) was added to plates and incubated for 30 minutes at room temperature. Stop Solution (2 N H_2SO_4) was then added to the wells and a yellow color reaction was read at 450 nm with A correction at 570 nm. Mean absorbance was determined from triplicate data readings and the mean background was subtracted. IL-1β concentration values were obtained from the standard curve. Inhibitory concentration of 50% (IC_{50}) was determined by comparing average IL-1β concentration to the positive control (THP-1 cells stimulated with opsonized zymosan). An average of n=4 replicate experiments was used to determine IC_{50} values for geldanamycin (IC_{50}=20 nM). See **FIG. 14**. The IC_{50} values for the following additional compounds were determined using this assay: IC_{50} (nM): mycophenolic acid 2888 nM); anisomycin, 127; rapamycin, 0.48; halofuginone, 919; IDN-6556, 642; epirubicin hydrochloride, 774; topotemay, 509; fascaplysin, 425; daunorubicin, 517; celastrol, 23; oxalipatin, 107; chromomycin A3, 148.

[**1168**] References: *J. Immunol.* (2000) 165: 411-418; *J. Immunol.* (2000) 164: 4804-4811; *J. Immunol Meth.* (2000) 235 (1-2): 33-40.

Example 48

Screening Assay for Assessing the Effect of Various Compounds on IL-8 Production by Macrophages

[**1169**] The human macrophage cell line, THP-1 was plated in a 12 well plate such that each well contains 1×10^6 cells in 2 mL of media containing 10% FCS. Opsonized zymosan was prepared by resuspending 20 mg of zymosan A in 2 mL of ddH_2O and homogenizing until a uniform suspension was obtained. Homogenized zymosan was pelleted at 250 g, resuspended in 4 mL of human serum for a final concentration of 5 mg/mL, and incubated in a 37° C. water bath for 20 minutes to enable opsonization. Geldanamycin was prepared in DMSO at a concentration of 10^{-2} M and serially diluted 10-fold to give a range of stock concentrations (10^{-8} M to 10^{-2} M).

[**1170**] THP-1 cells were stimulated to produce IL-8 by the addition of 1 mg/mL opsonized zymosan. Geldanamycin was added to THP-1 cells by directly adding DMSO stock solutions, prepared earlier, at a 1/1000 dilution, to each well. Each drug concentration was tested in triplicate wells. Plates were incubated at 37° C. for 24 hours.

[**1171**] After a 24 hour stimulation, supernatants were collected to quantify IL-8 production. IL-8 concentrations in the supernatants were determined by ELISA using recombinant human IL-8 to obtain a standard curve. A 96-well MAXISORB plate was coated with 100 μl of anti-human IL-8 Capture Antibody diluted in Coating Buffer (0.1M sodium carbonate pH 9.5) overnight at 4° C. The dilution of Capture Antibody used was lot-specific and was determined empirically. Capture antibody was then aspirated and the plate washed 3 times with Wash Buffer (PBS, 0.05% TWEEN-20). Plates were blocked for 1 hour at room temperature with 200 μl/well of Assay Diluent (PBS, 10% FCS pH 7.0). After blocking, plates were washed 3 times with Wash Buffer. Standards and sample dilutions were prepared as follows: (a) sample supernatants were diluted 1/100 and 1/1000; (b) recombinant human IL-8 was prepared at 200 pg/mL and serially diluted to yield as standard curve of 3.1 pg/mL to 200 pg/mL. Sample supernatants and standards were assayed in triplicate and were incubated at room temperature for 2 hours after addition to the plate coated with Capture Antibody. The plates were washed 5 times and incubated with 100 μl of Working Detector

(biotinylated anti-human IL-8 detection antibody+avidin-HRP) for 1 hour at room temperature. Following this incubation, the plates were washed 7 times and 100 μl of Substrate Solution (Tetramethylbenzidine, H_2O_2) was added to plates and incubated for 30 minutes at room temperature. Stop Solution (2 N H_2SO_4) was then added to the wells and a yellow color reaction was read at 450 nm with A correction at 570 nm. Mean absorbance was determined from triplicate data readings and the mean background was subtracted. IL-8 concentration values were obtained from the standard curve. Inhibitory concentration of 50% (IC_{50}) was determined by comparing average IL-8 concentration to the positive control (THP-1 cells stimulated with opsonized zymosan). An average of n=4 replicate experiments was used to determine IC_{50} values for geldanamycin (IC_{50}=27 nM). See **FIG. 15**. The IC_{50} values for the following additional compounds were determined using this assay: IC_{50} (nM): 17-AAG, 56; mycophenolic acid, 549; resveratrol, 507; rapamycin, 4; 41; SP600125, 344; halofuginone, 641; D-mannose-6-phosphate, 220; epirubicin hydrochloride, 654; topotemay, 257; mithramycin, 33; daunorubicin, 421; celastrol, 490; chromomycin A3, 36.

[1172] References: *J. Immunol.* (2000) 165: 411-418; *J. Immunol.* (2000) 164: 4804-4811; *J. Immunol Meth.* (2000) 235 (1-2): 33-40.

Example 49

Screening Assay for Assessing the Effect of Various Compounds on MCP-1 Production by Macrophages

[1173] The human macrophage cell line, THP-1 was plated in a 12 well plate such that each well contains 1×10^6 cells in 2 mL of media containing 10% FCS. Opsonized zymosan was prepared by resuspending 20 mg of zymosan A in 2 mL of ddH_2O and homogenizing until a uniform suspension was obtained. Homogenized zymosan was pelleted at 250 g and resuspended in 4 mL of human serum for a final concentration of 5 mg/mL and incubated in a 37° C. water bath for 20 minutes to enable opsonization. Geldanamycin was prepared in DMSO at a concentration of 10^{-2} M and serially diluted 10-fold to give a range of stock concentrations (10^{-8} M to 10^{-2} M).

[1174] THP-1 cells were stimulated to produce MCP-1 by the addition of 1 mg/mL opsonized zymosan. Eldanamycin was added to THP-1 cells by directly adding DMSO stock solutions, prepared earlier, at a 1/1000 dilution, to each well. Each drug concentration was tested in triplicate wells. Plates were incubated at 37° C. for 24 hours.

[1175] After a 24 hour stimulation, supernatants were collected to quantify MCP-1 production. MCP-1 concentrations in the supernatants were determined by ELISA using recombinant human MCP-1 to obtain a standard curve. A 96-well MaxiSorb plate was coated with 100 μl of anti-human MCP-1 Capture Antibody diluted in Coating Buffer (0.1M Sodium carbonate pH 9.5) overnight at 4° C. The dilution of Capture Antibody used was lot-specific and was determined empirically. Capture antibody was then aspirated and the plate washed 3 times with Wash Buffer (PBS, 0.05% TWEEN-20). Plates were blocked for 1 hour at room temperature with 200 μl/well of Assay Diluent (PBS, 10% FCS pH 7.0). After blocking, plates were washed 3 times with Wash Buffer. Standards and sample dilutions were prepared as follows: (a) sample supernatants were diluted 1/100 and 1/1000; (b) recombinant human MCP-1 was prepared at 500 pg/mL and serially diluted to yield as standard curve of 7.8 pg/mL to 500 pg/mL. Sample supernatants and standards were assayed in triplicate and were incubated at room temperature for 2 hours after addition to the plate coated with Capture Antibody. The plates were washed 5 times and incubated with 100 μl of Working Detector (biotinylated anti-human MCP-1 detection antibody+avidin-HRP) for 1 hour at room temperature. Following this incubation, the plates were washed 7 times and 100 μl of Substrate Solution (tetramethylbenzidine, H_2O_2) was added to plates and incubated for 30 minutes at room temperature. Stop Solution (2 N H_2SO_4) was then added to the wells and a yellow color reaction was read at 450 nm with A correction at 570 nm. Mean absorbance was determined from triplicate data readings and the mean background was subtracted. MCP-1 concentration values were obtained from the standard curve. Inhibitory concentration of 50% (IC_{50}) was determined by comparing average MCP-1 concentration to the positive control (THP-1 cells stimulated with opsonized zymosan). An average of n=4 replicate experiments was used to determine IC_{50} values for geldanamycin (IC_{50}=7 nM). See **FIG. 16**. The IC_{50} values for the following additional compounds were determined using this assay: IC_{50} (nM): 17-AAG, 135; anisomycin, 71; mycophenolic acid, 764; mofetil, 217; mitoxantrone, 62; chlorpromazine, 0.011; 1-α-25 dihydroxy vitamin D_3, 1; Bay 58-2667, 216; 15-deoxy prostaglandin J2, 724; rapamycin, 0.05; CNI-1493, 0.02; BXT-51072, 683; halofuginone, 9; CYC 202, 306; topotemay, 514; fascaplysin, 215; podophyllotoxin, 28; gemcitabine, 50; puromycin, 161; mithramycin, 18; daunorubicin, 570; celastrol, 421; chromomycin A3, 37; vinorelbine, 69; tubercidin, 56; vinblastine, 19; vincristine, 16.

[1176] References: *J. Immunol.* (2000) 165: 411-418; *J. Immunol.* (2000) 164: 4804-4811; *J. Immunol Meth.* (2000) 235 (1-2): 33-40.

Example 50

Screening Assay for Assessing the Effect of Paclitaxel on Cell Proliferation

[1177] Smooth muscle cells at 70-90% confluency were trypsinized, replated at 600 cells/well in media in 96-well plates and allowed to attachment overnight. Paclitaxel was prepared in DMSO at a concentration of 10^{-2} M and diluted 10-fold to give a range of stock concentrations (10^{-8} M to 10^{-2} M). Drug dilutions were diluted 1/1000 in media and added to cells to give a total volume of 200 μl/well. Each drug concentration was tested in triplicate wells. Plates containing cells and paclitaxel were incubated at 37° C. for 72 hours.

[1178] To terminate the assay, the media was removed by gentle aspiration. A 1/400 dilution of CYQUANT 400×GR

dye indicator (Molecular Probes; Eugene, Oreg.) was added to 1× Cell Lysis buffer, and 200 μl of the mixture was added to the wells of the plate. Plates were incubated at room temperature, protected from light for 3-5 minutes. Fluorescence was read in a fluorescence microplate reader at 480 nm excitation wavelength and ~520 nm emission maxima. Inhibitory concentration of 50% (IC_{50}) was determined by taking the average of triplicate wells and comparing average relative fluorescence units to the DMSO control. An average of n=3 replicate experiments was used to determine IC_{50} values. See **FIG. 17** (IC_{50}=7 nM). The IC_{50} values for the following additional compounds were determined using this assay: IC_{50} (nM): mycophenolic acid, 579; mofetil, 463; doxorubicin, 64; mitoxantrone, 1; geldanamycin, 5; anisomycin, 276; 17-AAG, 47; cytarabine, 85; halofuginone, 81; mitomycin C, 53; etoposide, 320; cladribine, 137; lovastatin, 978; epirubicin hydrochloride, 19; topotemay, 51; fascaplysin, 510; podophyllotoxin, 21; cytochalasin A, 221; gemcitabine, 9; puromycin, 384; mithramycin, 19; daunorubicin, 50; celastrol, 493; chromomycin A3, 12; vinorelbine, 15; idarubicin, 38; nogalamycin, 49; itraconazole, 795; 17-DMAG, 17; epothilone D, 5; tubercidin, 30; vinblastine, 3; vincristine, 9.

[1179] This assay also may be used assess the effect of compounds on proliferation of fibroblasts and murine macrophage cell line RAW 264.7. The results of the assay for assessing the effect of paclitaxel on proliferation of murine RAW 264.7 macrophage cell line were shown in **FIG. 18** (IC_{50}=134 nM).

[1180] Reference: *In vitro toxicol.* (1990) 3: 219; *Biotech. Histochem.* (1993) 68: 29; *Anal. Biochem.* (1993) 213: 426.

Example 51

Perivascular Administration of Paclitaxel to Assess Inhibition of Fibrosis

[1181] WISTAR rats weighing 250-300 g are anesthetized by the intramuscular injection of Innovar (0.33 ml/kg). Once sedated, they are then placed under halothane anesthesia. After general anesthesia is established, fur over the neck region is shaved, the skin clamped and swabbed with betadine. A vertical incision is made over the left carotid artery and the external carotid artery exposed. Two ligatures are placed around the external carotid artery and a transverse arteriotomy is made. A number 2 French Fogarty balloon catheter is then introduced into the carotid artery and passed into the left common carotid artery and the balloon is inflated with saline. The catheter is passed up and down the carotid artery three times. The catheter is then removed and the ligature is tied off on the left external carotid artery.

[1182] Paclitaxel (33%) in ethelyne vinyl acetate (EVA) is then injected in a circumferential fashion around the common carotid artery in ten rats. EVA alone is injected around the common carotid artery in ten additional rats. (The paclitaxel may also be coated onto an EVA film which is then placed in a circumferential fashion around the common carotid artery.) Five rats from each group are sacrificed at 14 days and the final five at 28 days. The rats are observed for weight loss or other signs of systemic illness. After 14 or 28 days the animals are anesthetized and the left carotid artery is exposed in the manner of the initial experiment. The carotid artery is isolated, fixed at 10% buffered formaldehyde and examined for histology. A statistically significant reduction in the degree of initimal hyperplasia, as measured by standard morphometric analysis, indicates a drug induced reduction in fibrotic response.

Example 52

In Vivo Evaluation of Silk Coated Perivascular PU Films to Assess the Ability of an Agent to Induce Scarring

[1183] A rat carotid artery model is described for determining whether a substance stimulates fibrosis. Wistar rats weighing 300 g to 400 g are anesthetized with halothane. The skin over the neck region is shaved and the skin is sterilized. A vertical incision is made over the trachea and the left carotid artery is exposed. A polyurethane film covered with silk strands or a control uncoated PU film is wrapped around a distal segment of the common carotid artery. The wound is closed and the animal is recovered. After 28 days, the rats are sacrificed with carbon dioxide and pressure-perfused at 100 mmHg with 10% buffered formaldehyde. Both carotid arteries are harvested and processed for histology. Serial cross-sections can be cut every 2 mm in the treated left carotid artery and at corresponding levels in the untreated right carotid artery. Sections are stained with H&E and Movat's stains to evaluate tissue growth around the carotid artery. Area of perivascular granulation tissue is quantified by computer-assisted morphometric analysis. Area of the granulation tissue is significantly higher in the silk coated group than in the control uncoated group. See **FIG. 19**. Other compounds may also be tested in this manner to assess their ability to induce scarring.

Example 53

In Vivo Evaluation of Perivascular PU Films Coated with Different Silk Suture Material to Assess Scarring

[1184] A rat carotid artery model is described for determining whether a substance stimulates fibrosis. Wistar rats weighing 300 g to 400 g are anesthetized with halothane. The skin over the neck region is shaved and the skin is sterilized. A vertical incision is made over the trachea and the left carotid artery is exposed. A polyurethane film covered with silk sutures from one of three different manufacturers (3-0 Silk—Black Braided (Davis & Geck), 3-0 SOFSILK (U.S. Surgical/Davis & Geck), and 3-0 Silk—Black Braided (LIGAPAK) (Ethicon, Inc.) is wrapped around a distal segment of the common carotid artery. (The polyurethane film can also be coated with other agents to induce fibrosis.) The wound is closed and the animal is allowed to recover.

[1185] After 28 days, the rats are sacrificed with carbon dioxide and pressure-perfused at 100 mmHg with 10%

buffered formaldehyde. Both carotid arteries are harvested and processed for histology. Serial cross-sections are cut every 2 mm in the treated left carotid artery and at corresponding levels in the untreated right carotid artery. Sections are stained with H&E and Movat's stains to evaluate tissue growth around the carotid artery. Area of perivascular granulation tissue is quantified by computer-assisted morphometric analysis. Thickness of the granulation tissue is the same in the three groups showing that tissue proliferation around silk suture is independent of manufacturing processes. See **FIG. 20**.

Example 54

In Vivo Evaluation of Perivascular Silk Powder to Assess the Capacity of an Agent to Induce Scarring

[**1186**] A rat carotid artery model is described for determining whether a substance stimulates fibrosis. Wistar rats weighing 300 g to 400 g are anesthetized with halothane. The skin over the neck region is shaved and the skin is sterilized. A vertical incision is made over the trachea and the left carotid artery is exposed. Silk powder is sprinkled on the exposed artery that is then wrapped with a PU film. Natural silk powder or purified silk powder (without contaminant proteins) is used in different groups of animals. Carotids wrapped with PU films only are used as a control group. The wound is closed and the animal is allowed to recover. After 28 days, the rats are sacrificed with carbon dioxide and pressure-perfused at 100 mmHg with 10% buffered formaldehyde. Both carotid arteries are harvested and processed for histology. Serial cross-sections can be cut every 2 mm in the treated left carotid artery and at corresponding levels in the untreated right carotid artery. Sections are stained with H&E and Movat's stains to evaluate tissue growth around the carotid artery. Area of tunica intima, tunica media and perivascular granulation tissue is quantified by computer-assisted morphometric analysis.

[**1187**] The natural silk caused a severe cellular inflammation consisting mainly of a neutrophil and lymphocyte infiltrate in a fibrin network without any extracellular matrix or blood vessels. In addition, the treated arteries were seriously damaged with hypocellular media, fragmented elastic laminae and thick intimal hyperplasia. Intimal hyperplasia contained many inflammatory cells and was occlusive in 2/6 cases. This severe immune response was likely triggered by antigenic proteins coating the silk protein in this formulation. On the other end, the regenerated silk powder triggered only a mild foreign body response surrounding the treated artery. This tissue response was characterized by inflammatory cells in extracellular matrix, giant cells and blood vessels. The treated artery was intact. These results show that removing the coating proteins from natural silk prevents the immune response and promotes benign tissue growth. Degradation of the regenerated silk powder was underway in some histology sections indicating that the tissue response can likely mature and heal over time. See **FIG. 21**.

Example 55

In Vivo Evaluation of Perivascular Talcum Powder to Assess the Capacity of an Agent to Induce Scarring

[**1188**] A rat carotid artery model is described for determining whether a substance stimulates fibrosis. Wistar rats weighing 300 g to 400 g are anesthetized with halothane. The skin over the neck region is shaved and the skin is sterilized. A vertical incision is made over the trachea and the left carotid artery is exposed. Talcum powder is sprinkled on the exposed artery that is then wrapped with a PU film. Carotids wrapped with PU films only are used as a control group. The wound is closed and the animal is recovered. After 1 or 3 months, the rats are sacrificed with carbon dioxide and pressure-perfused at 100 mmHg with 10% buffered formaldehyde. Both carotid arteries are harvested and processed for histology. Serial cross-sections are cut every 2 mm in the treated left carotid artery and at corresponding levels in the untreated right carotid artery. Sections are stained with H&E and Movat's stains to evaluate tissue growth around the carotid artery. Thickness of tunica intima, tunica media and perivascular granulation tissue is quantified by computer-assisted morphometric analysis. Histopathology results and morphometric analysis showed the same local response to talcum powder at 1 month and 3 months. A large tissue reaction trapped the talcum powder at the site of application around the blood vessel. This tissue was characterized by a large number of macrophages within a dense extracellular matrix with few neutrophiles, lymphocytes and blood vessels. The treated blood vessel appeared intact and unaffected by the treatment. Overall, this result showed that talcum powder induced a mild long-lasting fibrotic reaction that was subclinical in nature and did not harm any adjacent tissue. See **FIG. 22**.

Example 56

MIC Determination by Microtitre Broth Dilution Method

[**1189**] A. MIC Assay of Various Gram Negative and Positive Bacteria

[**1190**] MIC assays were conducted essentially as described by Amsterdam, D. 1996, "Susceptibility testing of antimicrobials in liquid media", p. 52-111, in Loman, V., ed. Antibiotics in laboratory medicine, 4th ed. Williams and Wilkins, Baltimore, Md. Briefly, a variety of compounds were tested for antibacterial activity against isolates of *P. aeruginosa, K. pneumoniae, E. coli, S. epidermidis* and *S. aureus* in the MIC (minimum inhibitory concentration assay under aerobic conditions using 96 well polystyrene microtitre plates (Falcon 1177), and Mueller Hinton broth at 37° C. incubated for 24 h. (MHB was used for most testing except C721 (*S. pyogenes*), which used Todd Hewitt broth, and *Haemophilus influenzae*, which used *Haemophilus* test medium (HTM)) Tests were conducted in triplicate. The results are provided below in Table 1.

TABLE 1

MINIMUM INHIBITORY CONCENTRATIONS OF THERAPEUTIC AGENTS AGAINST VARIOUS GRAM NEGATIVE AND POSITIVE BACTERIA

	Bactrial Strain					
Drug	*P. aeruginosa* PAE/K799 H187 Wt Gram−	*K. pneumoniae* ATCC13883 C238 wt Gram−	*E. coli* UB1005 C498 wt Gram−	*S. aureus* ATCC25923 C622 wt Gram+	*S. epidermidis* C621 wt Gram+	*S. pyogenes* C721 wt Gram+
doxorubicin	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-7}
mitoxantrone	10^{-5}	10^{-6}	10^{-5}	10^{-5}	10^{-5}	10^{-6}
5-fluorouracil	10^{-5}	10^{-6}	10^{-6}	10^{-7}	10^{-7}	10^{-4}
methotrexate	N	10^{-6}	N	10^{-5}	N	10^{-6}
etoposide	N	10^{-5}	N	10^{-5}	10^{-6}	10^{-5}
camptothecin	N	N	N	N	10^{-4}	N
hydroxyurea	10^{-4}	N	N	N	N	10^{-4}
cisplatin	10^{-4}	N	N	N	N	N
tubercidin	N	N	N	N	N	N
2-mercaptopurine	N	N	N	N	N	N
6-mercaptopurine	N	N	N	N	N	N
cytarabine	N	N	N	N	N	N

Activities are in Molar concentrations
Wt = wild type
N = No activity

[1191] B. MIC of Antibiotic-Resistant Bacteria

[1192] Various concentrations of the following compounds, mitoxantrone, cisplatin, tubercidin, methotrexate, 5-fluorouracil, etoposide, 2-mercaptopurine, doxorubicin, 6-mercaptopurine, camptothecin, hydroxyurea and cytarabine were tested for antibacterial activity against clinical isolates of a methicillin resistant *S. aureus* and a vancomycin resistant pediococcus clinical isolate in an MIC assay as described above. Compounds which showed inhibition of growth (MIC value of $<1.0\times10^{-3}$) included: mitoxantrone (both strains), methotrexate (vancomycin resistant pediococcus), 5-fluorouracil (both strains), etoposide (both strains), and 2-mercaptopurine (vancomycin resistant pediococcus).

Example 57

Preparation of Release Buffer

[1193] The release buffer is prepared by adding 8.22 g sodium chloride, 0.32 g sodium phosphate monobasic (monohydrate) and 2.60 g sodium phosphate dibasic (anhydrous) to a beaker. 1 L HPLC grade water is added and the solution is stirred until all the salts are dissolved. If required, the pH of the solution is adjusted to pH 7.4±0.2 using either 0.1N NaOH or 0.1N phosphoric acid.

Example 58

Release Study to Determine Release Profile of the Therapeutic Agent from a Coated Device

[1194] A sample of the therapeutic agent-loaded catheter is placed in a 15 ml culture tube. 15 ml release buffer (Example 57) is added to the culture tube. The tube is sealed with a TEFLON lined screw cap and is placed on a rotating wheel in a 37° C. oven. At various time points, the buffer is withdrawn from the culture tube and is replaced with fresh buffer. The withdrawn buffer is then analyzed for the amount of therapeutic agent contained in this buffer solution using HPLC.

[1195] All of the above U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet, are incorporated herein by reference, in their entirety.

[1196] From the foregoing, it is appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

1-1168. (canceled)

1169. A medical device, comprising a vagal nerve stimulator (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the medical device and the host into which the medical device is implanted.

1170. The medical device of claim 1169 wherein the agent inhibits cell regeneration.

1171. The medical device of claim 1169 wherein the agent inhibits angiogenesis.

1172. The medical device of claim 1169 wherein the agent inhibits fibroblast migration.

1173. The medical device of claim 1169 wherein the agent inhibits fibroblast proliferation.

1174. The medical device of claim 1169 wherein the agent inhibits deposition of extracellular matrix.

1175. The medical device of claim 1169 wherein the agent inhibits tissue remodeling.

1176. (canceled)

1177. (canceled)

1178. The medical device of claim 1169 wherein the agent is a chemokine receptor antagonist.

1179. The medical device of claim 1169 wherein the agent is a cell cycle inhibitor.

1180. The medical device of claim 1169 wherein the agent is a taxane.

1181. The medical device of claim 1169 wherein the agent is an anti-microtubule agent.

1182. The medical device of claim 1169 wherein the agent is paclitaxel.

1183. The medical device of claim 1169 wherein the agent is not paclitaxel.

1184. The medical device of claim 1169 wherein the agent is an analogue or derivative of paclitaxel.

1185. The medical device of claim 1169 wherein the agent is a vinca alkaloid.

1186. The medical device of claim 1169 wherein the agent is camptothecin or an analogue or derivative thereof.

1187. The medical device of claim 1169 wherein the agent is a podophyllotoxin.

1188. The medical device of claim 1169 wherein the agent is a podophyllotoxin, wherein the podophyllotoxin is etoposide or an analogue or derivative thereof.

1189. The medical device of claim 1169 wherein the agent is an anthracycline.

1190. The medical device of claim 1169 wherein the agent is an anthracycline, wherein the anthracycline is doxorubicin or an analogue or derivative thereof.

1191. The medical device of claim 1169 wherein the agent is an anthracycline, wherein the anthracycline is mitoxantrone or an analogue or derivative thereof.

1192. The medical device of claim 1169 wherein the agent is a platinum compound.

1193. The medical device of claim 1169 wherein the agent is a nitrosourea.

1194. The medical device of claim 1169 wherein the agent is a nitroimidazole.

1195. The medical device of claim 1169 wherein the agent is a folic acid antagonist.

1196. The medical device of claim 1169 wherein the agent is a cytidine analogue.

1197. The medical device of claim 1169 wherein the agent is a pyrimidine analogue.

1198. The medical device of claim 1169 wherein the agent is a fluoropyrimidine analogue.

1199. The medical device of claim 1169 wherein the agent is a purine analogue.

1200. The medical device of claim 1169 wherein the agent is a nitrogen mustard or an analogue or derivative thereof.

1201-1373. (canceled)

1374. The medical device of claim 1169, further comprising a second pharmaceutically active agent.

1375. (canceled)

1376. The medical device of claim 1169, further comprising an agent that inhibits infection.

1377-4842. (canceled)

4843. A method for inhibiting scarring comprising placing a vagal nerve stimulator (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent into an animal host, wherein the agent inhibits scarring.

4844. The method of claim 4843 wherein the agent inhibits cell regeneration.

4845. The method of claim 4843 wherein the agent inhibits angiogenesis.

4846. The method of claim 4843 wherein the agent inhibits fibroblast migration.

4847. The method of claim 4843 wherein the agent inhibits fibroblast proliferation.

4848. The method of claim 4843 wherein the agent inhibits deposition of extracellular matrix.

4849. The method of claim 4843 wherein the agent inhibits tissue remodeling.

4850. (canceled)

4851. (canceled)

4852. The method of claim 4843 wherein the agent is a chemokine receptor antagonist.

4853. The method of claim 4843 wherein the agent is a cell cycle inhibitor.

4854. The method of claim 4843 wherein the agent is a taxane.

4855. The method of claim 4843 wherein the agent is an anti-microtubule agent.

4856. The method of claim 4843 wherein the agent is paclitaxel.

4857. The method of claim 4843 wherein the agent is not paclitaxel.

4858. The method of claim 4843 wherein the agent is an analogue or derivative of paclitaxel.

4859. The method of claim 4843 wherein the agent is a vinca alkaloid.

4860. The method of claim 4843 wherein the agent is camptothecin or an analogue or derivative thereof.

4861. The method of claim 4843 wherein the agent is a podophyllotoxin.

4862. The method of claim 4843 wherein the agent is a podophyllotoxin, wherein the podophyllotoxin is etoposide or an analogue or derivative thereof.

4863. The method of claim 4843 wherein the agent is an anthracycline.

4864. The method of claim 4843 wherein the agent is an anthracycline, wherein the anthracycline is doxorubicin or an analogue or derivative thereof.

4865. The method of claim 4843 wherein the agent is an anthracycline, wherein the anthracycline is mitoxantrone or an analogue or derivative thereof.

4866. The method of claim 4843 wherein the agent is a platinum compound.

4867. The method of claim 4843 wherein the agent is a nitrosourea.

4868. The method of claim 4843 wherein the agent is a nitroimidazole.

4869. The method of claim 4843 wherein the agent is a folic acid antagonist.

4870. The method of claim 4843 wherein the agent is a cytidine analogue.

4871. The method of claim 4843 wherein the agent is a pyrimidine analogue.

4872. The method of claim 4843 wherein the agent is a fluoropyrimidine analogue.

4873. The method of claim 4843 wherein the agent is a purine analogue.

4874. The method of claim 4843 wherein the agent is a nitrogen mustard or an analogue or derivative thereof.

4875-5021. (canceled)

5022. The method of claim 4843, wherein the composition further comprises a second pharmaceutically active agent.

5023. (canceled)

5024. The method of claim 4843, wherein the composition further comprises an agent that inhibits infection.

5025-8647. (canceled)

8648. A method for making a medical device comprising: combining a vagal nerve stimulator (i.e., an electrical device) and an anti-scarring agent or a composition comprising an anti-scarring agent, wherein the agent inhibits scarring between the device and a host into which the device is implanted.

8649. The method of claim 8648 wherein the agent inhibits cell regeneration.

8650. The method of claim 8648 wherein the agent inhibits angiogenesis.

8651. The method of claim 8648 wherein the agent inhibits fibroblast migration.

8652. The method of claim 8648 wherein the agent inhibits fibroblast proliferation.

8653. The method of claim 8648 wherein the agent inhibits deposition of extracellular matrix.

8654. The method of claim 8648 wherein the agent inhibits tissue remodeling.

8655. (canceled)

8656. (canceled)

8657. The method of claim 8648 wherein the agent is a chemokine receptor antagonist.

8658. The method of claim 8648 wherein the agent is a cell cycle inhibitor.

8659. The method of claim 8648 wherein the agent is a taxane.

8660. The method of claim 8648 wherein the agent is an anti-microtubule agent.

8661. The method of claim 8648 wherein the agent is paclitaxel.

8662. The method of claim 8648 wherein the agent is not paclitaxel.

8663. The method of claim 8648 wherein the agent is an analogue or derivative of paclitaxel.

8664. The method of claim 8648 wherein the agent is a vinca alkaloid.

8665. The method of claim 8648 wherein the agent is camptothecin or an analogue or derivative thereof.

8666. The method of claim 8648 wherein the agent is a podophyllotoxin.

8667. The method of claim 8648 wherein the agent is a podophyllotoxin, wherein the podophyllotoxin is etoposide or an analogue or derivative thereof.

8668. The method of claim 8648 wherein the agent is an anthracycline.

8669. The method of claim 8648 wherein the agent is an anthracycline, wherein the anthracycline is doxorubicin or an analogue or derivative thereof.

8670. The method of claim 8648 wherein the agent is an anthracycline, wherein the anthracycline is mitoxantrone or an analogue or derivative thereof.

8671. The method of claim 8648 wherein the agent is a platinum compound.

8672. The method of claim 8648 wherein the agent is a nitrosourea.

8673. The method of claim 8648 wherein the agent is a nitroimidazole.

8674. The method of claim 8648 wherein the agent is a folic acid antagonist.

8675. The method of claim 8648 wherein the agent is a cytidine analogue.

8676. The method of claim 8648 wherein the agent is a pyrimidine analogue.

8677. The method of claim 8648 wherein the agent is a fluoropyrimidine analogue.

8678. The method of claim 8648 wherein the agent is a purine analogue.

8679. The method of claim 8648 wherein the agent is a nitrogen mustard or an analogue or derivative thereof.

8680-8855. (canceled)

8856. The method of claim 8648, wherein the medical device further comprises a second pharmaceutically active agent.

8857. (canceled)

8858. The method of claim 8648 wherein the medical device further comprises an agent that inhibits infection.

8859-13305. (canceled)

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摘要(译)

用于与组织接触的电气装置（例如，心律管理和神经刺激装置）与抗瘢痕形成剂（例如，细胞周期抑制剂）组合使用，以便抑制当将装置植入体内时可能发生的瘢痕形成。动物。