(19)日本国特許庁(JP)　(12)公表特許公報(A)　(11)特許出願公表番号
特表2004-533277
(P2004-533277A)
(43)公表日　平成16年11月4日(2004.11.4)

(51)Int.Cl.[7]	F I		テーマコード（参考）
A61L 27/00	A61L 27/00		4C060
A61B 17/00	A61B 17/00	320	4C076
A61K 9/06	A61K 9/06		4C081
A61K 9/10	A61K 9/10		4C084
A61K 9/14	A61K 9/14		4C086

審査請求 未請求　予備審査請求 未請求　（全 110 頁）　最終頁に続く

(21)出願番号　特願2002-563816(P2002-563816)
(86)(22)出願日　平成14年2月8日(2002.2.8)
(85)翻訳文提出日　平成15年8月11日(2003.8.11)
(86)国際出願番号　PCT/US2002/003726
(87)国際公開番号　WO2002/064014
(87)国際公開日　平成14年8月22日(2002.8.22)
(31)優先権主張番号　60/267,578
(32)優先日　平成13年2月9日(2001.2.9)
(33)優先権主張国　米国(US)

(71)出願人　502096886
エンドルミナル　セラピューティクス，インコーポレイテッド
アメリカ合衆国　アリゾナ　８５７５０，タクソン，　ノース　サミット　リッジ　ロード　５００１
(74)代理人　100078282
弁理士　山本　秀策
(74)代理人　100062409
弁理士　安村　高明
(74)代理人　100113413
弁理士　森下　夏樹

最終頁に続く

(54)【発明の名称】壁内療法

(57)【要約】
高分子材料を単独でか、または生体活性剤もしくは細胞と併用して、特に、開放外科的な適用、侵襲性を最小にした適用または経皮的な適用、経粘膜的な適用または経柔組織的な適用で、組織を治療または修復し、置き換え、移植しまたは増強する装置および方法が開発された。これらの方法および装置は、固形臓器または管状体構造の中心局面または壁内局面の機能を修復し、変えるか増強するのに有用である。１つの実施形態において、本発明の方法は、中間ゾーンに、治療剤および治療システムを堆積させる工程をさらに包含する。

【特許請求の範囲】
【請求項１】
損傷を最小にしつつ、臓器の本体、臓器要素または組織構造体を局所的に貫入し入り込んで、臓器の壁内ゾーンにアクセスする工程を包含する、治療の方法。
【請求項２】
中間ゾーンに、治療剤および治療システムを堆積させる工程をさらに包含する、請求項１に記載の方法。
【請求項３】
前記治療剤が、薬剤、細胞および重合体および診断装置および／または治療装置からなる群から選択される、請求項２に記載の方法。
【請求項４】
前記重合体が、分解性または非分解性であり得る、請求項３に記載の方法。
【請求項５】
前記重合体が、固体マトリックス、多孔性マトリックス、ヒドロゲル、オルガノゲル、コロイド状懸濁液、微粒子およびマイクロカプセル、アノ粒子およびそれらの組合せからなる群から選択される、請求項３に記載の方法。
【請求項６】
前記薬剤が、抗感染薬、抗真菌薬、駆虫薬、抗寄生虫薬、抗癌薬、抗増殖薬、抗移動薬、抗炎症薬、金属プロテアーゼ、プロテアーゼ、トロンビン分解薬、線維素溶解薬、ステロイド、ホルモン、ビタミン、炭水化物、脂質タンパク質、ペプチドおよび酵素からなる群から選択される、請求項３に記載の方法。
【請求項７】
前記薬剤が、ＰＤＧＦ、ＦＧＦ、ＴＧＦ、ＥＤＧＦ、Ｅｐｉｄｅｒｍａｌ　ＧＦ、ＮＧＦ、ＩＬＧＦ、Ｈｅｐａｔｏｃｙｔｅ散乱因子、血管形成成長因子、血清因子、コラーゲン、ラミニン、テネイシン、ＳＰＡＲＣ、トロンボスポンジン、フィブロネクチン、ビメンチンおよび他のマトリックス因子からなる群から選択される増殖成長因子である、請求項３に記載の方法。
【請求項８】
前記細胞が、同じ臓器の隣接正常ゾーンまたは異なる臓器の隣接正常ゾーンに由来の類似の自家細胞（すなわち、間葉細胞に対する間葉細胞）からなる群から選択される、請求項３に記載の方法。
【請求項９】
前記細胞が、同じ臓器の隣接正常ゾーンまたは異なる臓器の隣接正常ゾーンに由来の異なる自家細胞（すなわち、外胚葉細胞に対する間葉細胞または内皮細胞に対する脾細胞）からなる群から選択される、請求項３に記載の方法。
【請求項１０】
前記細胞が、幹細胞もしくは他の前駆細胞により産生されるか、または幹細胞もしくは他の前駆細胞の形状で産生される治療因子である、請求項３に記載の方法。
【請求項１１】
前記細胞が、移植前に、遺伝子変性なしでか、または遺伝的に変性してかのいずれかで外殖され、クローン的にかまたは別の方法で、移植用に、インビトロで膨張される、請求項３に記載の方法。
【請求項１２】
前記治療因子が、遺伝子、プラスミド、エピソーム、ウイルス、ウイロイド、または治療目的または合成目的用の他の微生物からなる群から選択される、請求項３に記載の方法。
【請求項１３】
前記治療因子が、熱ショックもしくは応力応答タンパク質、または熱ショックもしくは応力応答タンパク質の誘発物質である、請求項３に記載の方法。
【請求項１４】
前記壁内ゾーンに空洞または閉じ込め空間またはレザバ領域が存在しない場合、治療剤を

配置するために、このような空間を作り出す工程をさらに包含する、請求項１に記載の方法。
【請求項１５】
中空管状部材を含む装置であって、該中空管状部材は、末端貫入または切断手段、および治療剤を壁内組織に送達する手段を備え、該末端貫入または切断手段は、最小限の側副損傷を引き起こす、装置。
【請求項１６】
前記部材が、剛性であり、金属、重合体または複合材料から作製される、請求項１５に記載の装置。
【請求項１７】
前記部材が、可撓性であり、そしてカテーテル様装置を含む、請求項１５に記載の装置。
【請求項１８】
前記部材が、単一のレザバまたは複数のレザバに装着され、該レザバが、治療剤を閉じ込め送達する、請求項１５に記載の装置。
【請求項１９】
前記部材が、組織空間を作り出すために、その遠位末端に、膨張性カッターを有する、請求項１５に記載の装置。
【請求項２０】
診断用センサまたは治療用センサをさらに含む、請求項１５に記載の装置。
【請求項２１】
噴出手段をさらに含み、該噴出手段が、粒子を、前記壁内ゾーンに保持するために、外管腔または内管腔ゾーンを通って、弾道的に移動する、請求項１５に記載の装置。
【請求項２２】
前記噴出手段が、機械的加速、電気的移動、火花爆発およびガス爆発を含む群から選択される、請求項２１に記載の装置。
【請求項２３】
間接ガイド手段用または直接ガイド手段用の手段をさらに含む、請求項１５に記載の装置。
【請求項２４】
前記直接ガイド手段が、光ファイバー撮像システム、内視鏡、直接先端カメラ、ＣＣＤ、Ｃ－ＭＯＳまたは他のチップまたは電気ビデオシステム、超音波またはＧＰＳ位置決めシステムからなる群から選択される、請求項２３に記載の装置。
【請求項２５】
キットにおいて、電気活性剤を含有する空隙充填材料を備える、請求項１５に記載の装置。
【請求項２６】
空隙充填材料または移植片を含み、該空隙充填材料または移植片が、物理的、化学的または生物的情報を局所的に感知し、保存し、または遠隔計測できる、請求項１５に記載の装置。
【請求項２７】
電気活性または導電性重合体を含み、該重合体が、経皮的エネルギー送達により、直接または外部的に活性化されて、正または負の走電性（局所持続性または断続性の電流に基づいたそこからまたはそこへの組織治癒または細胞移動）を誘発する、請求項１５に記載の装置。
【請求項２８】
血管形成または筋形成を誘発する治療剤を含む、請求項１５に記載の装置。
【請求項２９】
血管形成成長因子、炎症性血管形成重合体または重合体構築物、電気活性または他のマイクロ傷害性または局所刺激重合体からなる群から選択される治療剤を含む、請求項２８に記載の装置。

【請求項３０】
内皮細胞、ＥＣ骨髄前駆細胞、他の幹細胞平滑筋細胞または前駆体、組合せ、神経細胞または神経幹細胞または上記の組合せからなる群から選択される細胞を含む、請求項２８に記載の装置。
【請求項３１】
神経再生のための、請求項１５に記載の装置。
【請求項３２】
生体活性重合体を含む、請求項１５に記載の装置。
【請求項３３】
応力応答誘発剤または実応力応答タンパク質を含む、請求項１５に記載の装置。
【発明の詳細な説明】
【背景技術】
【０００１】
（発明の背景）
本発明は、臓器または臓器要素の組織をインサイチュで操作する局面、または組織の中間面または壁内（ｅｎｄｏｍｕｒａｌ）面を標的にした操作によって、機能を修復し、設置するか、変更する局面に関する。
【０００２】
本願は、２００１年２月９日に出願された米国特許出願第６０／２６７，５７８号から優先権を主張している。
【０００３】
本発明は、具体的には、単独でか、または生体活性剤もしくは細胞と併用して、装置、高分子材料を外科的または経皮的のいずれかによって適用することにより、臓器、臓器要素または組織の壁内ゾーン（中間ゾーン）にアクセスすることにより、組織を治療または修復する装置、材料および方法に関する。
【０００４】
多くの疾患には、臓器の中心局面（例えば、肝臓の腫瘍、動脈壁内のアテローム硬化型外傷、前立腺の腺腫、脳内の悪性腫瘍など）が関与している。今日、これらの型の外傷の大部分は、開放外科的処置、侵襲性を最小にした処置または経皮的処置（これは、外管腔（ｅｃｔｏｌｕｍｉｎａｌ）または内管腔（ｅｎｄｏｌｕｍｉｎａｌ）面で始まって、臓器を直接切開する）によって、除去される。そういうものとして、これらのアプローチは、病気に罹ったゾーンを除去または治療する過程において、病気に冒されていない周囲の組織層にて、多くの健康な組織を除去する。例えば、臓器内腫瘍の開放外科的除去では、含まれる疾患ゾーンを除去する過程において、そのカプセルゾーンおよび外管腔ゾーンだけでなく、それを取り囲む健康な壁内ゾーンも、しばしば、犯され切開される。この療法は、有効であるものの、「選択的」破壊または治療というよりもむしろ、「集団」の罹患率の負担を加える。
【０００５】
不要な組織損傷および除去という同じ問題は、経皮的または管腔内でアクセスされ治療される疾患についても当てはまる。この経路によって管腔内領域にアクセスすると、伝統的に、疾患に罹ったゾーンに行き着くために、その上に横たわる管腔内層およびそれを取り囲む壁内の健康なゾーンが除去される。この一例は、前立腺腫の現在の治療であるＴＵＲＰ（前立腺の経尿道切除）処置で、見られ得る。ＴＵＲＰでは、臓器内に含まれる腺腫にアクセスして除去するために、尿道周囲のカラムだけでなく、正常な尿路上皮性の粘膜層も除去される。この方法は、そこに含まれる疾患ゾーンを除去するのに有効であるものの、残念なことに、同時に、相当量の正常な非疾患組織を除去する。そういうものとして、現在の処置は、それらの侵襲性およびそれに付随した外傷が原因で、不要な罹患率および死亡率をもたらす。
【０００６】
現在の療法の他の制約は、現在の療法がしばしば外部の内管腔ゾーンまたは外管腔ゾーン

のいずれかだけを治療するのに対して、壁内ゾーンでは、細胞の攪乱が関与しているという事実にある。この一例は、冠状動脈および末梢動脈のアテローム硬化型外傷の治療で見られ得る。重症のアテローム硬化型閉塞の場合には、しばしば、血管内アテローム切除術、カテーテルベースのシェイビング、コアリングまたは穿孔手順により、血管内から閉塞性外傷を血管内除去することが使用されている。これらの方法は、血管の管腔に近く治療装置に近い患部アテロームを除去する。しかしながら、それらは、その疾患の源または「中心」（これは、しばしば、動脈の媒体、血管の壁内ゾーンにある）に取り組まない。

【０００７】

今日の多くの療法は、局所臓器内効果を達成するという目標で、全身的に投与される。もし、機械的で物理的な標的化を行うシステムおよび方法が、同時の持続的な臓器内存在をさらに効果的にして、存在しているなら、部位特異的療法が達成される。多くの「局所」療法は、局所ではあるが限局性ではなく、実際、隣接したゾーンに影響を与える。この一例には、肝臓内悪性腫瘍（例えば、肝細胞腫または肝転移）の動脈内化学療法がある。この療法では、その臓器内の疾患を治療するために、肝動脈または血管系システムを経由して、薬剤が投与されるが、実際、その臓器全体が医薬品に浸される。さらに別の肝臓送達される医薬品は、引き続いて、全身の血液と管腔内で直接拡散または混合する。

【発明の開示】

【発明が解決しようとする課題】

【０００８】

従って、本発明の目的は、周囲の組織に対する損傷を最小にして、病気に罹った臓器を治療する方法および装置を提供することにある。

【０００９】

本発明のさらなる目的は、周囲の組織に対する損傷を最小にして、病気に罹った臓器または組織の中心、コア、すなわちほぼ「壁内」のゾーンを治療する方法および装置を提供することにある。

【００１０】

本発明のさらなる目的は、全身的な毒性を回避しつつ、特定の組織を治療する方法および装置を提供することにある。

【００１１】

本発明の他の目的は、治癒を助けるために壁内で送達または放出できる高分子材料、薬剤および生体活性組成物を提供することにある。

【００１２】

本発明のなおさらなる目的は、外科的および経皮的の両方で、壁内組織にアクセスし変性し、および／または高分子材料、薬剤および生体活性組成物（これは、治癒を助けるために、壁内で送達または放出できる）を送達する装置を提供することにある。

【課題を解決するための手段】

【００１３】

（発明の要旨）

高分子材料を単独でまたは生体活性剤または細胞と併用して、特に、開放外科的な適用、侵襲性を最小にした適用または経皮的な適用、経粘膜的な適用または経柔組織的な適用で、組織を治療または修復し、置き換え、移植しまたは増強する装置および方法が開発された。これらの方法およびシステムは、固形臓器または管状体構造の中心局面または壁内局面の機能を修復し、変えるか増強するのに有用である。

【００１４】

（発明の詳細な説明）

壁内組織を治療する方法が開発された。この方法は、一般に、臓器内に管状組織アクセス装置（針、トロカール、カテーテル）を経皮的に設置する工程を包含する。この臓器では、組織が除去される。その穴には、流動性の前成形または乾燥したヒドロゲルまたは固形重合体プラグが設置され、その空隙を満たし、組織路を密封する。この方法は、種々の用途で有用である。例えば、心内膜（または心外膜）面は、送達装置を経由してアクセスさ

れるが、この装置は、心臓壁に接して安定化され、心筋が貫通されて、この壁内ゾーンにアクセスし、空間または空隙が作り出され、心筋には、細胞、重合体、薬剤および遺伝子またはこれらの組合せが、種々の順序で送達できる。次いで、この空隙の主要部またはプラグは、適当な位置で密封される。

【００１５】

この方法は、一般に、図１および図２Ａ～２Ｇで示されている。この方法は、以下の工程を包含する：

１．経皮的、外科的、腹腔鏡的、経血管的、経腸的、包膜内的、組織平面を経由する皮下的、経リンパ的などのいずれかで、臓器の近くにアクセスする工程。

【００１６】

２．その送達手段を適当な位置に置き安定化する工程。

【００１７】

３．内アクセスまたは外アクセスについて、管腔内ゾーンを貫入し、壁内ゾーンで安定化し、組織を局所的に治療し、そして組織を除去する工程（機械的、熱的、レーザー、高周波、紫外線、Ｘ線（組織を損傷する任意の形態）、電磁エネルギー、音響エネルギー（超音波）、乾燥、気体暴露（CO_2、エーテル）、化学的（代謝拮抗薬、抗新生物薬、抗炎症薬、抗微生物薬、抗ウイルス薬、抗生物質、ホルモン、抗体など））。

【００１８】

４．薬剤（例えば、薬理剤、細胞または他の生物製剤または医用生体材料）を送達する工程。

【００１９】

５．ゾーンを密封し路にアクセスする工程。

【００２０】

（定義）

（Ｉ．高等動物の一般組織）

高等動物（例えば、ヒトを含めた哺乳動物）の構造組織は、複数の一体化し相互作用する組織要素からなっている。これらの組織は、個別臓器として組織化され得、これらは、機能的工場（例えば、生化学的な媒介物を産生する肝臓）または装置システム（例えば、血液を機械的にポンプ上げする心臓および電気的に信号を送り事象を調整する脳）である。本明細書中で呼ぶ臓器とは、固形臓器および中空臓器（例えば、それぞれ、肝臓および結腸）を含む。

【００２１】

あるいは、動物は、組織要素を含み、これらは、大部分は、機能流体（例えば、血液、リンパ液、内分泌または外分泌の分泌物または気体）用の導管である。これらの管状「臓器要素」または導管は、動脈、静脈、リンパ管、胆管、尿管、ファロピウス管などのような構造体である。

【００２２】

（ＩＩ．臓器および臓器要素の構造－定義した壁内ゾーン）

個別臓器は、総称的に、３つの領域またはゾーンを有するとして記述され得る。これらの領域には、以下が挙げられる：１．外管腔または外部ゾーン（すなわち、カプセル、漿膜など）、２．壁内または中間ゾーン、および３．内管腔ゾーン。個別臓器では、外管腔領域は、典型的には、その臓器を保護して含めるように機能する。臓器の壁内ゾーンは、典型的には、臓器の機能末端、すなわち「ビジネス末端」であり、組織修復、臓器再生、代謝または他の特別な機能のために、防御細胞および修繕細胞用の恒常性タンパク質、ホルモン、酵素および免疫グロブリンを産生する生化学工場として作用する。機械力学的臓器（例えば、心臓および肺）では、その壁内ゾーンは、液体または気体を推進するか交換する機能を果たす。臓器の内部ゾーンまたは外管腔ゾーンは、壁内ゾーンと類似の機能を有し得るか、なお別の内部境界または障壁層として作用し得る。もし、臓器が断面で切断されると、その外管腔ゾーンは、１０％±１０の外部断面積として特徴付けられ得、その壁内ゾーンは、８０％±１０の中間断面積として特徴付けられ得、そして、その内管腔ゾー

ンは、１０％±１０の内部断面積として特徴付けられ得る。
【００２３】
固形臓器または中空臓器（これは、空洞を有する）に加えて、重要な身体構造として、真性管状臓器および臓器要素が存在している。管状臓器の例には、小腸および結腸が挙げられる。管状臓器要素には、臓器内で互いに貫入している主要な血管（例えば、肝臓の門脈、脳の海綿静脈洞）が挙げられる。管状組織構造体の例には、導管（例えば、胆管）または血管（例えば、動脈または静脈）が挙げられる。
【００２４】
管状臓器および組織構造体は、一般に、積層した多層「管内管」構造を有し、これは、少なくとも３層から構成される。これらの管状臓器、臓器要素または組織構造体の全ては、上記臓器について、外管腔ゾーン、壁内ゾーンおよび内管腔ゾーンに概説したのと類似の様式で、特徴付けられ得る。管状構造体では、この外管腔ゾーンは、１０％±１０の外部断面積として特徴付けられ得、その壁内ゾーンは、８０％±１０の中間断面積として特徴付けられ得、また、その内管腔ゾーンは、１０％±１０の内部断面積として特徴付けられ得る。興味深いことに、管状臓器および組織構造体は、規定の組織層を有し、これらは、一般に、これらのゾーンと相関している。この外管腔ゾーンは、漿膜または外膜と相関している。この壁内ゾーンは、固有層、粘膜下組織、筋肉または媒体と相関している。この内管腔ゾーンは、内膜または粘膜と相関している。
【００２５】
（治療方法）
（Ｉ．局在化治療）
臓器または組織の壁内領域の治療に集中する方法は、臓器または組織構造体の中心領域または壁内領域「内」にて、活性疾患を除去するか閉じ込めるか局所治療することに関連して、隣接、近接または「側副」する健康な組織に対する外傷を少なくする手段を提供する。これによりまた、その疾患を、全身暴露の危険なしで、薬剤、細胞またはシステムを使って、局所ベースで、さらに効果的に治療できるようになる。重合体、医薬品、遺伝子、治療用ペプチド、細胞、放射線システムなどを局所適用することにより、近接または隣接する周囲の健康な組織への暴露を行わずに、臓器の患部ゾーンに治療を集中できる。局所臓器内療法は、薬剤の全身暴露（これは、全身的に悪影響を及ぼし得る）を少なくする。これにより、全身的な薬剤の漏出による影響を減少させて、毒性を懸念することなく、より高い有効濃度の薬剤を適用できるようになる。
【００２６】
壁内治療はまた、持続的な局所療法を行う手段、ならびに全身送達で典型的な時間よりも長い時間にわたって、通常の非経口療法または局所療法と比較して、臓器内での閉じ込め、それゆえ、持続的な暴露または治療のための存在をもたらす。臓器内に空洞またはポケットを作り出すことにより、内部からの「再建」および再構成が可能となる。上に血流のない、「優先」ゾーンで治療薬または治療物質を配置すると、保持が高まり、それにより、それらの薬剤の作用を持続させる。これにより、また、さらに正確な治療がなされる。
【００２７】
壁内治療は、その治療の様相を局在化するだけでなく、疾患を物理的に遮断して、その疾患の局所療法、および疾患に対する障壁を作り出す。
【００２８】
（ＩＩ．シードベッドとしての臓器の壁内領域の使用）
壁内療法は、他の臓器で通常生じる他の機能を提供するために細胞または臓器要素を配置または移植するための土壌として、１つの臓器床または本体を利用する可能性をもたらす。多くの疾患状態では、臓器の生命機能は、疾患によって減退または破壊される。通常の療法は、生じる症状を薬理学的に制限することを目指しているか、または失われた機能を回復しようと試みている。これらの手法は、限られている。臓器の疾患にもかかわらず、残りの組織成分または間質は、しばしば、それ自体、関連した機能を有する。さらに、たとえ特定の臓器の特殊な組織および細胞が疾患に罹ったとしても、その臓器の血管、神経

および間質のマトリックスは、しばしば、無傷であり、機能的な一般臓器床である。これらの残りの構造は、細胞、細胞－重合体組合せ、他の臓器要素、類器官、人工臓器または生物反応器の移植（ｔｒａｎｓｐｌａｎｔａｔｉｏｎ　ｏｒ　ｉｍｐｌａｎｔａｔｉｏｎ）のための豊かな「土壌」と見なされ得る。これらの疾患に罹った臓器の外殻は、それらの移植片を移植する床に「ハウスキーピング」機能（すなわち、動脈および静脈供給、リンパ排液、神経支配などであり、これらは、既に内蔵されていて、無傷である）を提供するように機能する。

【００２９】

（ＩＩＩ．高分子構造材料または生体活性材料の適用）

上述のように、疾患を治療するために、または補助的な機能を提供するために、治療材料（例えば、薬剤および細胞）が投与でき、壁内に含有できる。他の材料（例えば、さらなる特性（例えば、治癒を促進し、炎症を最小にするか誘発し、線維性応答を少なくし、異常な増殖を阻止するか、他の治療上の利益をもたらす性能）を有する重合体）もまた、利用され得る。重合体それ自体が生体活性であり得るか、または包埋もしくは移植された生体活性分子、ペプチド、脂質、薬剤または他の部分を含有し得る。これらの重合体は、生体応答を抑制、維持または刺激し得る。これらの重合体はまた、組織ゾーンを分離する組織の接着剤、粘着剤または封止剤として働き得、内部障壁を作り出す。これらの重合体はまた、移植した細胞、断片または組織用の人工の生体分解性または永久的な足場または間質を提供するのに役立ち得る。

【００３０】

（ＩＶ．臓器にアクセスする方法）

臓器または組織は、開放露出により、または侵襲性を最小にした技術により、いずれかによって、外科的にアクセスできるか、または経皮的にアクセスできる。

【００３１】

臓器または組織の壁内領域はまた、内部臓器を開放露出することにより、または経体壁（ｔｒａｎｓ－ｂｏｄｙ　ｗａｌｌ）切開により、外科的にアクセスできる。これに続いて、典型的には、開放放射状切開なしで、臓器の規定の狭い集中穿刺が行われ、引き続いて、壁内ゾーンに入り、治療剤を配置する。

【００３２】

壁内には、典型的には、針、トロカール、弾道移動－爆発性弾丸様の火花発射、噴出ペレット（例えば、遺伝子銃）、空気移動（高圧空気、CO_2）、化学浸透、光学または他の照射をベースにした貫入、超音波、エレクトロポレーションまたはフェレーシスにより媒介される移動の使用により、入る。

【００３３】

これらの貫入の経路および手段は、侵襲性が最小であり、直接の組織接触によるか身体の内部への鍵穴または他の限定ポート侵入により、引き続いて規定される集中接触および類似の貫入手段を使うか臓器を引き続いて狭いまたは限られた物理的穿刺により、開放放射状切開なしで使用され得、引き続いて、治療剤を直接または上記限定貫入、浸透もしくは他の輸送手段により配置するために、壁内ゾーンに入り得る。

【００３４】

図３～５は、この目的のために使用され得る装置を示している。図３Ａは、簡単なバルーン装置を示し、ここで、カテーテル１０は、バルーン１２を含み、これは、送達される薬剤粒子１４に浸透性である。バルーン１２内の活性剤または推進剤または他の手段１６は、図３Ｂで示すように、バルーン１２から組織内へと薬剤粒子１４を推進するのに使用される。図３Ｂは、血管１８を示し、ここで、薬剤粒子１４は、壁内ゾーン２０内に包埋されている。

【００３５】

図４Ａで示した他の実施形態では、薬剤粒子１４は、以下により、壁内ゾーン内の所望位置に送達できる：組織管腔にカテーテル２２を導入することであって、ここで、カテーテル２２は、２個の膨張性部材２４および２６（典型的には、バルーン）を有し、そして２

個の部材２４および２６の間の空間に、薬剤粒子１４を送達する手段２８を有する；膨張性部材２４および２６を膨張して、この管腔の標的部分を閉塞し、アクチュエータ手段３０（これは、薬剤粒子１４を推進して、マクロ多孔膜３２に通し、壁内ゾーンに入れる）によって力を加えることにより薬剤粒子１４を投与し、膨張性部材２４および２６を収縮させ、そしてカテーテル２２を除去すること。好ましい１実施形態では、このカテーテルはまた、閉塞領域を洗い流すのに使用され、血管の場合、その領域は、実質的に血液がないようにされる。図４Ｂは、アクチュエータ手段３０の拡大図であり、これは、膨張性壁３２、先端３４（これは、このアクチュエータ手段を送達手段２８に挿入する）および推進手段３６を備えている。推進手段３６は、爆発手段、液圧手段、または他のエネルギー発生手段であり得る。

【００３６】

図５Ａで示すように、これらの薬剤粒子は、他の手段（例えば、圧電ポンプ４０）を使用して、送達できる。ポンプ４０は、ノズル４２を含み、これは、回転可能であり、そして適当な標的に薬剤を送達するように、曲げることができる。これは、カテーテル４４に装着され、このカテーテルは、図５Ｂで示すように、近位バルーン、遠位バルーン、ガイドワイヤ（または他の操縦手段）４６、および必要に応じて、１種以上の物質（洗浄液または灌注液、接着剤または重合体溶液を含めて）を分散させる手段４８など、および必要に応じて、物質を加熱する伝導手段５０を含む。

【００３７】

送達はまた、経皮経路により得、例えば、身体の導管系または「ハイウェイ」への経皮的な入口を通過し得る。直接の視覚的ガイド、蛍光ガイドまたは超音波ガイド下にて、所望対象領域に進み、引き続いて、壁内および／または管腔内ゾーンに入り、上で概説したように、必要に応じて、治療剤を配置する。

【００３８】

移植可能装置または送達手段には、データ測定用センサ、および／またはデータ分析器、および／またはデータ保存手段、および／またはデータ遠隔測定／伝達手段（情報転送の孤立レベルまたは入れ子レベルという複数のレベルで伝達する手段を含む）を挙げることができる。これらの装置は、これらのセンサを使用して行われる測定に応答して、移植片を改良する手段または応答（例えば、局所または全身薬剤送達）を備え付ける手段を組み込み得る。これらは、泌尿器学、肝臓学または心臓学で特に有用であり、この場合、それらの移植片は、時間の経過と共に変わる変数（例えば、圧力（これは、流体流れの変化を表示する）およびその移植片が配置される尿道、胆管または血管の直径）に応答性の１個またはそれ以上のセンサを含有する。患者の外側にあるモニタリング手段によるこれらのセンサからの直接または間接のいずれかのフィードバック、必要であり得る信号変化（例えば、この移植片の膨張であって、この場合、組織管腔の直径は、時間の経過と共に、変化する）があると、この移植片は、不安定になるか移動する。他の実施形態では、この移植片は、生体活性剤、予防薬、診断薬またはｐＨ変性剤を含有する。１実施形態では、この移植片は、温度またはｐＨが変わると薬剤が放出されるように、温度またはｐＨに応答性の物質から形成される。

【００３９】

これらのシステムはまた、遠隔データ記憶または操作システム（例えば、時計様装置、小型携帯装置、皮膚内または皮膚外移植片、電話システム装置（携帯電話、伝言サービス、ポケットベル、業務用ファックス機）、携帯型コンピュータ、携帯情報端末（ＰＤＡ、例えば、Ｐａｌｍ　Ｐｉｌｏｔ^{TM}システム）またはインターネット（ワールドワイドウェブ）またはコンピュータアクセス装置）に、医師または看護婦が移植片に遠隔で相互作用するのにモニターまたは使用できる装置を介して、患者を接続するのに使用できる。

【００４０】

（Ｖ．臓器に貯蔵ゾーンを作製する方法）

簡単なカテーテル、トロカールまたは針を挿入することにより、空隙が作り出され得る。この空隙は、その挿入装置と同じ大きさであり得る。あるいは、この空隙は、膨張性カッ

ターシステムにより、さらに大きく作製され得、これらは、放射状または円錐状または他の幾何学形状で、展開する。空隙はまた、他の機械的手段（例えば、組織モルセレータ、バルーン拡張器、機械的組織ジャッキまたはストレッチャー）、熱、電気、超音波レーザー、ＵＶ、Ｘ線、または他の傷害性または切除性の電磁放射線、極低温、化学物質（例えば、酸、アルカリ、洗剤）、浸透圧脆弱化手段、または酵素手段（例えば、パパイン、トリプシン、キモトリプシン、マトリックスメタロプロテイナーゼ、繊維分解剤、ストレプトキナーゼおよび組織プラスミノーゲン活性剤）によって、作製され得る。これらの空隙をさらに洗浄し拡張するために、吸引、灌流または超灌流が使用され得る。

【００４１】

空隙は、薬剤、重合体、重合体－薬剤混合物または共有結合した薬剤－重合体組合せで満たされ得る。重合体は、空隙形成剤を送達することにより空隙の形成をさらに促進するために、治療目的のために最初に作製された空隙を満たすために、段階的または連続的な治療計画で治療剤を引き続いて送達するために、空隙がさらに膨張するのを制限するために、引き続いた細胞または組織の移植用にネオマトリックスまたは足場を設けるために、もしくは空隙または空洞－障壁制限空隙の出入りを形成するために、使用され得る。さらに、これらの障壁は、単方向様式または双方向様式のいずれかで、選択的に浸透性であり得る。

【００４２】

重合体は、治療効果があり得るか、治療薬を送達する手段として働き得る。重合体は、装置を挿入することにより作製された、簡単な空間に挿入され得るか、組織の欠損、空隙または他の空洞を最初に作り出した結果として形成された大きい空間に挿入され得る。疾患、欠損または外科的処置の結果として形成された空隙は、接着性重合体（これは、空隙の空洞壁の結合および治癒を促進する）で満たされる。重合体は、特に、炎症、二次出血および後の線維性の瘢痕をできるだけ少なくするように選択される。あるいは、もし、血管形成応答または繊維形成応答が望ましいなら、重合体は、炎症誘発応答、血管形成応答、繊維形成応答を誘発するように選択され得る。

【００４３】

臓器内の組織の空洞は、空洞内組織結合剤として作用する生体適合性で生物分解性の重合体で満たすことができ、それにより、壁内管腔空間を同時に大きくしつつ、この空洞空間の崩壊および排除を可能にする。これらの重合体は、自然に固化し得るか、以下でさらに詳細に論述するように、適当な刺激に晒すと、重合するか組織に結合され得る。重合体は、漸進的な水の取り込みおよび空隙の収縮を促進するために、または組織を膨潤させる取り込みを防止するために、いずれかのために、「治療」性、吸湿性または疎水性を有し得る。これらの重合体は、炎症および後の線維性応答を最小にしつつ、治癒を促進するように選択される。組織にやさしい生物分解性の高分子生体接着剤を協調して使用することで、明らかな容量の低下、および直接組織切開により形成された空洞の閉塞が保証される。さらに、その中に薬剤、遺伝子または細胞を取り込んだ高分子材料は、例えば、治癒を促進するため、炎症および／またはコラーゲン堆積および瘢痕を減らすため、ならびにエンドクリン過程および局所成長制御を操作するために、相乗的な生化学および細胞療法を長期間にわたって送達する局所デポーとして働き得る。

【００４４】

（ＶＩ．臓器に移植する方法）

これらの物質は、上記のように作製された貯蔵ゾーンにて、臓器に直接移植できる。薬剤および重合体以外の移植物質には、細胞が挙げられる。細胞は、細胞培養物中か、インビトロで成長できるか、生検により得ることができる。細胞は、遺伝子的に改変され得る。細胞は、同系、同種異系または異種であり得る。同種異系または異種の細胞は、免疫寛容になるようにカプセル化され得る。

【００４５】

細胞は、単一細胞、単一細胞型または複数細胞型のスラリーとして加えられ得るか、複数の源、臓器断片または組織破片に由来し得る。所定臓器または臓器成分に加えられた細胞

は、同一または類似の分化した正常細胞、異なる分化した正常細胞、前駆細胞、遺伝的に形質移入、形質転換または操作した細胞、幹細胞、胚細胞、多分化性細胞、始原細胞、同種異系細胞、異種遺伝子型細胞、異種移植片細胞、カプセル化した同種異系細胞、異種遺伝子型細胞または異種移植片細胞であり得る。治療的な非哺乳類細胞、真核生物細胞、植物細胞または原核細胞は、送達され得る。

【００４６】

治療的な生物学的製剤（例えば、細胞断片、ヘテロカリオン、ウイルス、偽ビリオン、ウイロイド、プリオン、ＤＮＡまたはＲＮＡ（センス、アンチセンス、リボザイムまたはアプタマー（ａｐｔｅｍｅｒ））は、共に送達され得る。

【００４７】

植物細胞、原核細胞または人工細胞は、同様に治療に応じて、投与され得る。これらの細胞は、接種および経路指定をし易くするために、また、免疫拒絶反応を防止するために、受動化またはカプセル化され得る。

【００４８】

他の臓器での代替物として機能するために、１つの臓器からは、異なる臓器に由来の細胞または組織が移植され得る。例えば、血管形成前駆体として作用するように、肝臓の外殻または瘢痕または心筋瘢痕には、脾細胞が移植できる。糖尿病に罹った患者の心臓には、臨床的な危険信号の治療的に有益な返答として、アンギナの感覚を戻すために、神経幹細胞または後根神経節細胞を移植できる。血液前駆体として働くために、骨髄には、脾細胞が移植できる。

【００４９】

（ＶＩ．高分子材料またはヒドロゲル材料）

生物分解性材料および／または生体適合性材料は、治癒のために、空洞、管状臓器または臓器要素内で構造上の支持を与えるために、手術および／または薬剤送達に続いた他の管腔または空洞を支持する必要性を助けるかなくすために、壁内治療装置により作製された空隙、空洞、チャンネルまたは他の空間を満たし、成形し、増大させるか、付着させるのに使用され得る。例えば、高分子材料またはヒドロゲル材料は、組織の過剰増殖または炎症により引き起こされる障害を治療するために、組織の除去により作製される空洞の表面または内部で適用できる。これらの材料は、組織空洞の側面を共に付着させ、（例えば、炎症プロセスをできるだけ少なくするために）組織表面の１つまたはそれ以上の表面で障壁を形成し、生体活性剤を送達し、放射性同位体、放射線不透過性微粒子などを保持するのに使用できる。その重合体は、上述のように、そのカテーテルの表面または先端から、血管または臓器の壁内組織の内部で展開され得る。あるいは、この重合体は、長い可撓性の管状装置（これは、特定の用途が指示するできるだけ多くの管腔からなる）を経由して、噴霧、押出により適用できるか、またはそうでなければ内部送達できる。

【００５０】

好ましくは、その方法は、特定の分解、寿命および特性を備えた生体分解性または生体腐食性の合成重合体または天然重合体を利用し、これらは、厚さ、長さおよび三次元形状（例えば、点、星形、線状、円筒形、アーチ形、螺旋、８の字形など）を変えて、特注設計で適用できる。そのプロセスの治療剤送達機能は、多数の複雑な臓器または血管の表面の内部に適応する「特注可能」展開形状性能と容易に組み合わされ得る。例えば、重合体は、単一重合体層または複数重合体層のいずれかの形状で適用でき、複数の重合体層を使用するとき、異なる重合体層で適用することにより、異なる薬物が投与できる。

【００５１】

（１．高分子材料の選択）

その目的（例えば、構造、接着性、障壁または薬剤送達）に依存して、種々の異なる材料が使用できる。構造が要求される用途には、適当な機械的特性および物理的特性を有する重合体が選択される。この重合体は、用途に従って望ましいように組織を形成するために必要な時間にわたって生体分解性であることが好ましい。これは、数日、数週間または数ヶ月であり得る。これらの高分子材料の有利な点は、良好な流れ特性または他の組織適合

性を有する平滑な平面を維持しつつ、その重合体を平坦でない表面の割れ目に形づくるように仕立てることができることにある。組織の狭小化は、もし起こるなら、狭小化をさらに加速することなく、その初期手順に続いて、６ヶ月のウィンドウを超えて安定化する傾向にある。最適には、もし、異質な支持装置または封止材料を組織に導入するなら、主に、治癒およびピーク炎症反応中にて、意図した効果を発揮する必要がある。本明細書中では、主に、高分子材料を参照して記述されているものの、他の材料もまた使用され得ることが理解できるはずである。例えば、比較的に分子量が低い有機化合物（例えば、通常の糖（例えば、スクロース））（濃厚な暖かい水溶液から注型されて、その場で、モノリシック固形物として構成され、膨張を最小にしつつ腐食または断片化する）が、高分子材料の代わりに使用され得る。イオン交換で形成される無機化合物（例えば、ポリケイ酸塩、分解性バイオセラミックスおよび「プラスター」（これらは、表面腐食により分解するが、その場で、硬化する））もまた、使用できる。

【００５２】

その目的が構造支持特性を必要としない用途には、その重合体は、生体接着性の材料または特定分子量の分子を不浸透性の材料、または非常に浸透性で取り込まれた薬剤を所望時間にわたって放出する、重合体の単一層程度の少ない層からなり得る材料から形成され得る。

【００５３】

従って、使用する高分子材料の性質は、それが、被覆、絆創膏、接着剤、薬剤送達装置または機械的支持体の役割を果たすかどうかにより、決定される。さらに、重合体の選択は、望ましくない反応を防止することを目標とする時間にわたって、適切な生体分解速度に対して必要とされる、構造上および形状の完全性の程度を適切に釣り合わせなければならない。ある場合には、その材料は、その重合体の最終インビボ形状が重合体被覆の最終機能を支配する場合、同一または異なる目的であり得る。薄層で適用することで、その重合体フィルムは、被覆、封止剤および／または分割障壁、絆創膏および薬剤デポーとして機能できる。厚い層の重合体の複雑な内部適用により、実際、高い構造支持が得られ得、その層で使用する重合体の量に依存して、実際、血管または臓器開存性を維持する機械的な役割を果たす。例えば、殆どが線維筋性の成分から構成された組織の外傷は、高い程度の粘弾性反跳を有する。これらの外傷または組織は、さらに高い構造上の安定性を与えるような、厚さまたは剛性および程度が高い壁内コーティングを塗布するプロセスを使用する必要があり、それにより、血管の放射状の圧縮力に耐える。これにより、構造上の安定性が得られ、一般に、全ての管状の生物学的臓器または基礎構造の管腔内形状を維持するのに適用できる。

【００５４】

この高分子材料のための基本的要件は、生体適合性であり、そして以下の性能である：固形状態または流動状態で適用され、次いで、非流動性高分子材料（これは、機械的強度、浸透性、接着性および／または取り込まれた物質の放出の点から、規定された特性を有する）が得られるようにインビボで達成できる条件下にて、化学的または物理的に再構成する性能。

【００５５】

これらの高分子材料は、重合体、モノマー、マクロマーまたはそれらの組合せとして適用でき、溶液、懸濁液または分散液として維持され、本明細書中では、他に述べられていなければ、一緒にして、「溶液」と呼ぶ。高分子材料は、遊離ラジカルまたはイオンの形成（例えば、光重合によって）に応答して、熱硬化性、熱可塑性、重合可能であり得、化学的またはイオン的（すなわち、グルタルアルデヒドまたはイオン（例えば、カルシウムイオン）のような試薬を使用することによる）に架橋可能であり得る。これらの高分子材料を凝固または重合する手段の例には、単独で、または追加触媒の存在下で、または内生手段（例えば、生理学的ｐＨへの変更、カルシウムイオン（例えば、アルギン酸塩）もしくはホウ酸塩イオン（例えば、ポリビニルアルコール）の高分子材料への拡散、または体温（３７℃）への温度の変化）により、外生手段の適用（例えば、光、超音波、放射線また

はキレート化の適用）が挙げられる。

【００５６】

非生体分解材料または生体分解材料のいずれかが使用できるが、生体分解材料が好ましい。本明細書中で使用する「生体分解性」とは、インビボ条件下にて、典型的には、１年未満（さらに典型的には、数ヶ月または数週間未満）の期間にわたって、加水分解、酸化開裂または酵素作用により、さらに小さい単位に分解する物質を記述すると解釈される。炎症、拡大および／または過剰増殖を防止するために組織に適用するには、移植後、６ヶ月で実質的に分解する重合体を使用するのが好ましい。接着を防止するか放出を制御するために、分解が起こる時間は、治癒に必要な時間（すなわち、一般に、２週間より長いが、６ヶ月未満）と相関しているべきである。

【００５７】

適切な材料は、市販されているか、当業者に公知の方法を使用して、容易に合成できる。これらの材料には、以下が挙げられる：溶解性および不溶性で生体分解性および非生体分解性の天然または合成の重合体。これらは、ヒドロゲルまたは熱可塑性物質、単独重合体、共重合体またはブレンド（天然または合成）であり得る。本明細書中で使用する、ヒドロゲルは、織り交ぜ重合体成分（好ましくは、その重量の９０％の水）を有する水相として、定義される。以下の定義は、Ｄｉｃｔｉｏｎａｒｙ ｏｆ Ｃｈｅｍｉｃａｌ Ｔｅｒｍｓ，第４版、ＭｃＧｒａｗ Ｈｉｌｌ（１９８９）：Ｈｙｄｒｏｇｅｌに由来している：コロイドは、その分散相（コロイド）が連続相（水）と混ざって、粘性のゼリー状生成物（例えば、凝固したケイ酸）を生成する。オルガノゲルは、織り交ぜ重合体成分（好ましくは、その重量の９０％の有機溶媒）を有する有機相として、定義される。好ましい溶媒には、非毒性の有機溶媒（例えば、ジメチルスルホキシド（ＤＭＳＯ））、および鉱油および植物油が挙げられる。好ましい重合体は、合成重合体であり、インサイチュで形成可能または合成可能であり、合成特性および分解特性が制御されている。

【００５８】

代表的な天然重合体には、タンパク質（例えば、ゼイン、変性ゼイン、カゼイン、ゼラチン、グルテン、血清アルブミンまたはコラーゲン）および多糖類（例えば、セルロース、デキストラン、ヒアルロン酸、アクリル酸エステルおよびメタクリル酸エステルの重合体、およびアルギン酸）が挙げられる。これらは、その最終生成物の特性および投与に続く分解の高レベルの変化のために、好ましくない。合成的に改変した天然重合体には、アルキルセルロース、ヒドロキシアルキルセルロース、セルロースエーテル、セルロースエステルおよびニトロセルロース、生体重合体に不飽和を導入するための上記天然重合体のアクリル酸エステルまたはメタクリル酸エステルが挙げられる。

【００５９】

代表的な合成重合体には、ポリエステル、ポリホスファジン、ポリ（ビニルアルコール）、ポリアミド、ポリカーボネート、ポリアルキレン、ポリアクリルアミド、ポリアルキレングリコール、ポリアルキレンオキシド、ポリアルキレンテレフタレート、ポリビニルエーテル、ポリビニルエステル、ポリビニルハライド、ポリビニルピロリドン、ポリシロキサン、ポリウレタンおよびそれらの共重合体が挙げられる。他の重合体には、セルロース（例えば、メチルセルロース、エチルセルロース、ヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロース、ヒドロキシブチルメチルセルロース、酢酸セルロース、プロピオン酸セルロース、酢酸酪酸セルロース、酢酸フタル酸セルロース、カルボキシメチルセルロース、三酢酸セルロース、硫酸セルロースナトリウム塩）、アクリレート（例えば、ポリ（メタクリル酸メチル）、ポリ（メタクリル酸エチル）、ポリ（メタクリル酸ブチル）、ポリ（メタクリル酸ヘキシル）、ポリ（メタクリル酸イソデシル）、ポリ（メタクリル酸ラウリル）、ポリ（メタクリル酸フェニル）、ポリ（アクリル酸メチル）、ポリ（アクリル酸イソプロピル）、ポリ（アクリル酸イソブチル）、ポリ（アクリル酸オクタデシル））、ポリエチレン、ポリプロピレン、ポリ（エチレングリコール）、ポリ（エチレンオキシド）、ポリ（酢酸ビニル）、ポリ塩化ビニル、ポリスチレン、ポリビニルピロリドンおよびポリビニルフェノールが挙げられる。代表的な生体腐食性重合体には、

ポリラクチド、ポリグリコリドおよびそれらの共重合体、ポリ（ヒドロキシ酪酸）、ポリ（ヒドロキシ吉草酸）、ポリ（ラクチド－ｃｏ－カプロラクトン）、ポリ［ラクチド－ｃｏ－グリコリド］、ポリ無水物、ポリオルトエステル、それらのブレンドおよび共重合体が挙げられる。

【００６０】

これらの重合体は、Ｓｉｇｍａ　Ｃｈｅｍｉｃａｌ　Ｃｏ．（Ｓｔ．Ｌｏｕｉｓ，ＭＯ．）、Ｐｏｌｙｓｃｉｅｎｃｅｓ（Ｗａｒｒｅｎｔｏｎ，ＰＡ）、Ａｌｄｒｉｃｈ（Ｍｉｌｗａｕｋｅｅ，ＷＩ．）、Ｆｌｕｋａ（Ｒｏｎｋｏｎｋｏｍａ，ＮＹ．）およびＢｉｏＲａｄ（Ｒｉｃｈｍｏｎｄ，ＣＡ．）のような業者から得ることができるか、または他に、これらの業者から得られるモノマーから標準的な技術を使用して合成できる。

【００６１】

これらの材料は、さらに、以下のように分類できる。温度の関数として重合するか粘度が変わる材料。

【００６２】

ポリ（オキシアルキレン）重合体および共重合体（例えば、ポリ（エチレンオキシド）ポリ（プロピレンオキシド）（ＰＥＯ－ＰＰＯ）共重合体）、およびこれらの重合体とポリ（α－ヒドロキシ酸）（これには、乳酸、グリコール酸およびヒドロキシ酪酸、ポリカルボラクトンおよびポリバレロラクトンが挙げられるが、これらに限定されない）のような重合体との共重合体およびブレンドは、合成できるか、市販されている。例えば、ポリオキシアルキレン共重合体は、米国特許第３，８２９，５０６号；同第３，５３５，３０７号；同第３，０３６，１１８号；同第２，９７９，５７８号；同第２，６７７，７００号；および同第２，６７５，６１９号で記述されており、その教示内容は、本明細書中で参考として援用されている。ポリオキシアルキレン共重合体は、Ｐｌｕｒｏｎｉｃ^{TM}の商品名で、ＢＡＳＦおよび他の企業により販売されている。好ましい材料には、Ｆ－１２７、Ｆ－１０８、および他のゲル材料（Ｆ－６７）との混合物が挙げられる。これらの材料は、室温またはそれより低い温度では、粘性溶液として適用され、それより高い体温では、固化する。他の例には、低Ｔｍおよび低Ｔｇ等級のスチレン－ブタジエン－スチレンブロック共重合体（Ｐｏｌｙｍｅｒ　Ｃｏｎｃｅｐｔ　Ｔｅｃｈｎｏｌｏｇｉｅｓ製、Ｃ－ｆｌｅｘ^{TM}）がある。高温で液状であるが体温では固形である重合体溶液もまた、利用できる。例えば、インビボ用の熱硬化性で生体分解性の重合体は、Ｄｕｎｎらの米国特許第４，９３８，７６３号で記述されている。

【００６３】

カルシウム、バリウム、マグネシウム、銅および鉄を含めたいくつかの二価イオンは、体組織および血液の通常の成分である。これらのイオンは、以下のような重合体をイオン的に架橋するように使用できる：天然に生じる重合体であるコラーゲン、フィブリン、エラスチン、アガロース、寒天、多糖類（例えば、ヒアルロン酸、ヒアロビウロン酸、ヘパリン、セルロース、アルギン酸塩、カードラン、キチンおよびキトサン、およびそれらの誘導体）、酢酸セルロース、カルボキシメチルセルロース、ヒドロキシメチルセルロース、硫酸セルロースナトリウム塩、およびエチルセルロース。超音波または放射線で光化学的に架橋できる材料。

【００６４】

光、超音波または放射線を使用して架橋できる材料は、一般に、二重結合または三重結合を含有し、好ましくは、その二重結合または三重結合に結合した電子吸引基を有する材料である。適切な材料の例には、ポリ（アクリル酸）に重合されるモノマー（すなわち、Ｃａｒｂｏｐｏｌｓ（登録商標））、ポリ（アクリレート）、ポリアクリルアミド、ポリビニルアルコール、アクリル化ポリエチレングリコールおよびエチレンビニルアクリレートが挙げられる。光重合には、光増感剤、光開始剤またはそれらの両方が存在している必要があり、これは、光開始重合の速度を速くするか、重合が起こる波長をシフトするか、いずれかの任意の物質である。オレフィン性モノマーの放射線分解により、カチオン、アニオンおよび遊離ラジカルが形成され、これらの全ては、連鎖重合、グラフト化および架橋

を開始し、光重合と同じ重合体を重合するのに使用できる。光重合はまた、シクロ二量体化可能な系（例えば、クマル酸およびケイ皮酸誘導体）に適切な波長を適用することにより、誘発できる。α－ヒドロキシ酸骨格は、カルボニウムイオンに活性化できる。引き続いて反応してアミン含有配位子を形成できるＣＯＯＨまたはSO_3H官能性が挿入できる。グルタルアルデヒドのような共有結合架橋剤を付加することにより架橋できる物質。

【００６５】

任意のアミノ含有重合体は、ジアルデヒド（例えば、グルタルアルデヒドまたはスクシンジアルデヒド）を使用して、共有結合的に架橋できる。有用なアミノ含有重合体の例には、ポリペプチドおよびタンパク質（例えば、アルブミンおよびポリエチレンイミン）が挙げられる。下記のような特殊な機能を有するペプチドもまた、例えば、重合中にて、架橋剤を使用して、これらの物質に共有結合できる。

【００６６】

遊離カルボン酸または他のアニオン性基（例えば、スルホン酸）を有する重合体（例えば、上記アクリル酸重合体）は、組織接着性を高めるために、単独で使用できるか、他の重合体処方物に加えることができる。あるいは、この高分子材料には、組織結合特性を有する材料が付加または結合できる。組織結合特性を有するペプチドは、以下で述べる。高分子材料に共有結合して、それをムチンおよび粘膜細胞層に特異性に標的できるレクチンが使用できる。有用なレクチン配位子には、以下から単離したレクチンが挙げられる：Ａｂｒｕｓ ｐｒｅｃａｔｒｏｉｕｓ、Ａｇａｒｉｃｕｓ ｂｉｓｐｏｒｕｓ、Ａｎｇｕｉｌｌａ ａｎｇｕｉｌｌａ、Ａｒａｃｈｉｓ ｈｙｐｏｇａｅａ、Ｐａｎｄｅｉｒａｅａ ｓｉｍｐｌｉｃｉｆｏｌｉａ、Ｂａｕｈｉｎｉａ ｐｕｒｐｕｒｅａ、Ｃａｒａｇａｎａ ａｒｏｂｒｅｓｃｅｎｓ、Ｃｉｃｅｒ ａｒｉｅｔｉｎｕｍ、Ｃｏｄｉｕｍ ｆｒａｇｉｌｅ、Ｄａｔｕｒａ ｓｔｒａｍｏｎｉｕｍ、Ｄｏｌｉｃｈｏｓ ｂｉｆｌｏｒｕｓ、Ｅｒｙｔｈｒｉｎａ ｃｏｒａｌｌｏｄｅｎｄｒｏｎ、Ｅｒｙｔｈｒｉｎａ ｃｒｉｓｔａ ｇａｌｌｉ、Ｅｕｏｎｙｍｕｓ ｅｕｒｏｐａｅｕｓ、Ｇｌｙｃｉｎｅ ｍａｘ、Ｈｅｌｉｘ ａｓｐｅｒｓａ、Ｈｅｌｉｘ ｐｏｍａｔｉａ、Ｌａｔｈｙｒｕｓ ｏｄｏｒａｔｓ、Ｌｅｎｓ ｃｕｌｉｎａｒｉｓ、Ｌｉｍｕｌｕｓ ｐｏｌｙｐｈｅｍｕｓ、Ｌｙｓｏｐｅｒｓｉｃｏｎ ｅｓｃｕｌｅｎｔｕｍ、Ｍａｃｌｕｒａ ｐｏｍｉｆｅｒａ、Ｍｏｍｏｒｄｉｃａ ｃｈａｒａｎｔｉａ、Ｍｙｃｏｐｌａｓｍａ ｇａｌｌｉｓｅｐｔｉｃｕｍ、Ｎａｊａ ｍｏｃａｍｂｉｑｕｅ、ならびに、ｌｅｃｔｉｎｓ Ｃｏｎｃａｎａｖａｌｉｎ Ａ、Ｓｕｃｃｉｎｙｌ－Ｃｏｎｃａｎａｖａｌｉｎ Ａ、Ｔｒｉｔｉｃｕｍ ｖｕｌｇａｒｉｓ、Ｕｌｅｘ ｅｕｒｏｐａｅｕｓ Ｉ、ＩＩおよびＩＩＩ、Ｓａｍｂｕｃｕｓ ｎｉｇｒａ、Ｍａａｃｋｉａ ａｍｕｒｅｎｓｉｓ、Ｌｉｍａｘ ｆｌｕｖｕｓ、Ｈｏｍａｒｕｓ ａｍｅｒｉｃａｎｕｓ、Ｃａｎｃｅｒ ａｎｔｅｎｎａｒｉｕｓ、およびＬｏｔｕｓ ｔｅｔｒａｇｏｎｏｌｏｂｕｓ。

【００６７】

任意の微小球体または重合体鎖に、正に荷電した任意の配位子（例えば、ポリエチレンイミン、ポリリシンまたはキトサン）を結合すると、粘液の正味の負電荷に対するカチオン性基の静電引力が原因で、生体付着性が向上し得る。正電荷および疎水性コアを有する界面活性剤様分子は、その二層膜と適合性である。この分子は、そのコアおよび正電荷を分散して、相互エネルギーを最小にし、それにより、さらに高い組織接着性となる。そのムチン層のムコ多糖類およびムコタンパク質（特に、シアル酸残基）は、負に荷電した表面層を担う。ムチンとの結合親和性が高い任意の配位子もまた、この高分子材料に共有結合できる。

【００６８】

高分子材料はまた、組織接着剤としても使用できる。１つの形態では、フィブリンが使用される。これは、トロンビンおよび塩化カルシウムを添加することにより、患者自身のフィブリノーゲン、血液または血清を使用して、インサイチュで容易に形成できるという有利な点がある。上記材料もまた、使用できる。他の市販の重合体組織接着剤には、シアノアクリレート接着剤、ＧＲＦ（ゼラチン－レゾルシノール－ホルムアルデヒド）およびポ

リエチレングリコールポリ（乳酸および／またはグリコール酸）－アクリレート（両方とも、液体として適用され、次いで、光重合される）が挙げられる。

【００６９】

この高分子材料は、空洞または組織内の材料を制御するか取り込まれた材料を放出するかいずれかのために、浸透性を制御するように設計できる。管腔内に存在している材料に関して、基本的に、その高分子材料を設計する３つの状況がある：管腔から、この高分子材料を通って、組織管腔面へと、事実上、栄養分（低分子量成分）および気体のみを通過させる；栄養分、気体および巨大分子（大きいタンパク質および殆どのペプチドを含めて）を通過させる；そして栄養分、気体、巨大分子および細胞を通過させる。これらの材料の分子量範囲は、公知であり、従って、所望の多孔度を計算するのに使用できる。例えば、巨大分子は、１０００ダルトンより大きい分子量を有するとして定義される；細胞は、一般に、６００～７００ｎｍ～から１０ミクロンまでの範囲であり、３０～４０ミクロンの大きさの凝集物である。細胞を通過させるには、この材料は、マクロポーラス構造を有するかそれを生じなければならない。

【００７０】

（重合に続いて容量が減少する材料の形成）

特定の状況下において、例えば、壁を共に保持する空洞用の接着剤として塗布する溶液よりも小さい容量を占める重合体をインサイチュで生成することが有用であり得る。この重合は、重合中にて、その重合体から水を「シネレシス」、すなわち、駆出することにより、達成できる。その生成物の質量を少なくすることの他に、このプロセスは、治癒に望まれ得る多孔性生成物を生じ得る。シネレシスは、重合反応が１単位容量あたり多数の部分基（ｆｒａｃｔｉｏｎ　ｇｒｏｕｐ）の反応と共に起こるとき（高架橋密度、または反応物の希釈溶液が重合されて、その処方物中の水の量が、得られる重合体の固有膨潤能力を超えるとき）、起こる。後者は、例えば、ＰＥＧ－ジアクリレートの希釈溶液を重合するとき、起こり得る（例えば、５％以下のマクロマー）。

【００７１】

（ＶＩＩ．生体活性剤の取り込み）

この高分子材料には、広範囲の生体活性剤を取り込むことができる。これらは、この高分子材料に、物理的または化学的に取り込むことができる。物理的に取り込んだ材料の放出は、その高分子材料の拡散および／または分解により、達成される；化学的に取り込んだ材料の放出は、その重合体または重合体に生体活性物質をカップリングする化学結合の分解により、達成される（例えば、ペプチドは、酵素（例えば、トリプシン、トロンビンまたはコラゲナーゼ）により、インビボで開裂される）。ある場合には、この生体活性剤は、永久的に、または高分子材料が分解してその部位から取り除かれるまで、長期間にわたって、この高分子材料と会合したままであるのが望まれ得る。

【００７２】

最も広い意味では、これらの生体活性物質には、タンパク質（これは、本明細書中で定義したように、一般に、他に特定されていなければ、１００個未満のアミノ酸からなるように構成されたペプチドを含む）、糖類、多糖類および炭水化物、核酸、および合成有機物質および無機物質、またはそれらの組合せを挙げることができる。

【００７３】

特定の物質には、抗生物質、抗ウイルス薬、抗炎症薬（ステロイドおよび非ステロイドの両方）、抗悪性腫瘍薬、鎮痙薬（チャンネル遮断薬を含めて）、細胞－細胞外マトリックス相互作用の変調剤（細胞成長阻害剤および抗付着分子を含めて）、酵素および酵素阻害剤、抗凝血剤、成長因子、ＤＮＡ、ＲＮＡアンチセンス、リボザイム、アプタマーおよびタンパク質合成阻害剤、抗細胞移動剤、抗増殖剤、血管拡張薬、および組織の傷害を処置するのに通例使用される他の薬剤が挙げられる。これらの化合物の例には、アンジオテンシン転換酵素阻害剤、抗血栓薬、プロスタサイクリン、ヘパリン、サリチレート、血栓溶解薬、抗増殖薬、硝酸塩、カルシウムチャンネル遮断薬、ストレプトキナーゼ、ウロキナーゼ、組織プラスミノーゲン活性化剤（ＴＰＡ）およびアニソレート（ａｎｉｓｏｙｌａ

ｔｅｄ）プラスミノーゲン活性化剤（ＴＰＡ）およびアニソレートプラスミノーゲンーストレプトキナーゼ活性化剤錯体（ＡＰＳＡＣ）、ＧＰＩＩｂ／ＩＩＩＡアンタゴニスト、コルヒチンおよびアルキル化剤、成長変調因子（例えば、インターロイキン）、形質変換成長因子－β、および血小板由来成長因子の同属種、線維芽細胞成長因子、上皮細胞成長因子、肝細胞散乱因子、レプチン（ｌｅｐｔｉｎ）、成長因子に対して指向されるモノクローナル抗体、変性細胞外マトリックス成分またはそれらのレセプター、脂質およびコレステロール封鎖剤、マトリックス金属プロテアーゼ（ＭＭＰ）、コラゲナーゼ、プラスミンおよび他の薬剤（これは、組織のトーン、機能を変調し得る）、ならびに処置後の臓器損傷に対する治癒応答が挙げられる。このような化合物のさらなる例には、一酸化窒素含有物、放出物質または生成物質、抗増殖薬、および酸化防止剤（その多くは、公知である）が挙げられる。

【００７４】

ホルモン、特に、生殖ホルモンまたは性ホルモンは、これらの物質を使用して送達するに、特に有利である。それはまた、化学療法薬（例えば、ＢＣＮＵ、シスプラチン、タキソール、Ａｃｔｉｎｏｍｙｃｉｎ Ｄおよび他の細胞毒性薬）を送達するのに有用であり得る。また、ストレス応答誘発剤を加えて、熱ショックまたは他の哺乳動物のストレスタンパク質応答を誘起することも、望まれ得る。薬剤には、有機および無機のマンガン、スズ、カドミウム化合物、ゲルダナマイシン（ｇｅｌｄａｎａｍｙｃｉｎ）および類似の酸化剤（例えば、過酸化水素）が挙げられる。さらなるストレス応答タンパク質もまた、投与され得る。特定の状況では、これらの誘発物質およびストレス応答の阻害剤もまた、送達され得る。

【００７５】

結合ペプチド（例えば、ＦＮ細胞結合テトラペプチドＡｒｇ－Ｇｌｙ－Ａｓｐ－Ｓｅｒ（ＲＧＤＳ））、セレクチンレセプタ、および特定の細胞型（例えば、白血球および血小板）を誘因し結合するよう作用する炭化水素分子（例えば、Ｓｉａｌｙｌ Ｌｅ．ｓｕｐ．ｘ．）のような物質が使用され得る。フィブロネクチン、ビメンチンおよびコラーゲンのような物質は、細胞型を非特異的に結合して治癒を向上させるのに使用され得る。官能性ＲＧＤ配列を運ぶことが公知の他のタンパク質には、血小板接着タンパク質フィブリノーゲン、ビトロネクチンおよびｖｏｎ Ｗｉｌｌｅｂｒａｎｄ因子、オステオポンチンおよびラミニンが挙げられる。特定のＲＧＤペプチドは、米国特許第４，５１７，６８６号（Ｒｕｏｓｌａｈｔｉら）、同第４，５８９，８８１号（Ｐｉｅｒｓｃｈｂａｃｈｅｒら）、同第５，１６９，９３０号（Ｒｕｏｓｌａｈｔｉら）、同第５，１４９，７８０号（Ｐｌｏｗら）、同第４，５７８，０７９号（Ｒｕｏｓｌａｈｔｉら）、同第５，０４１，３８０号（Ｒｕｏｓｌａｈｔｉら）、ならびにＰｉｅｒｓｃｈｂａｃｈｅｒおよびＲｕｏｓｌａｈｔｉ，Ｊ．Ｂｉｏｌ．Ｃｈｅｍ．２６２（３６），１７２９４～１７２９８（１９８７）、Ｍｏｈｒｉら、Ａｍｅｒ．Ｊ．Ｈｅｍ．３７：１４～１９（１９９１）、Ａｕｍａｉｌｌｅｙら、ＦＥＢＳ ２９１（１），５０～５４（１９９１）、Ｇｕｒｒａｔｈら、Ｅｕｒ．Ｊ．Ｂｉｏｃｈｅｍ．２１０，９１１～９２１（１９９２）、およびＳｃａｒｂｏｒｏｕｇｈら、Ｊ．Ｂｉｏｌ．Ｃｈｅｍ．２６８（２），１０６６～１０７３（１９９３）に記載されている。ラミニンは、細胞の接着、移動、分化、および増殖を促進する（Ｋｌｅｉｎｍａｎら、Ｊ．Ｃｅｌｌ Ｂｉｏｃｈｅｍ．２７：３１７～３２５（１９８５）；Ｋｌｅｉｎｍａｎら、Ｂｉｏｃｈｅｍ．２５：３１２～３１８（１９８６）；Ｂｅｃｋら、ＦＡＳＥＢ Ｊ．４：１４８～１６０（１９９０））。ノナペプチドＣＤＰＹＩＧＳＲは、細胞の接着および移動を促進する（Ｇｒａｆら、Ｃｅｌｌ ４８：９８９～９９６（１９８７），Ｂｉｏｃｈｅｍ．２６：６８９６～６９００（１９８７））。さらに他の研究は、ＹＩＧＳＲ含有ペプチドが血管形成および腫瘍転移を阻止し得ることを示した（Ｇｒａｎｔら、Ｃｅｌｌ ５８：９３３～９４３（１９８９）、Ｉｗａｍｏｔｏら、Ｓｃｉｅｎｃｅ ２３８：１１３２～１１３４（１９８７）、Ｓａｋａｍｏｔｏら、Ｃａｎｃｅｒ Ｒｅｓ．５１：９０３～９０６（１９９１））。他のペプチドには、ＰＤＳＧＲおよびＩＫＶＡＶが挙げられる。インテグリンは、典型的には、かなり高度な保存配列

Ａｒｇ－Ｇｌｙ－Ａｓｐ　Ｘ（ＲＧＤＸ）（ここで、Ｘは、特定の細胞接着タンパク質に依存する変数である）によって、細胞接着タンパク質に結合する。

【００７６】

取り込まれる細胞には、間質細胞および／または線維芽細胞あるいは組織の空隙の閉合を促進する他の間葉細胞が挙げられる。あるいは、腺性上皮細胞（これは、成熟細胞か、発達細胞か、胚性／胎児細胞か、または遺伝的操作されて細胞のいずれかである）が堆積され得る。これらは、内分泌またはパラ分泌ホルモンもしくは他のメディエーターの放出によって、局地的または全身的な生理機能を変えるように働き得る。さらに、再神経支配および／または局所的なアドレナリン作用性応答、コリン作用性応答もしくは他の神経伝達物質応答を促進するために、神経細胞、前駆体または組織が移植され得る。

【００７７】

好ましい実施形態では、壁内ゾーンでの血管形成を誘導するかそのゾーンへの路にアクセスするための因子および細胞の組合せが使用される。代表的な血管新生成長因子には、ＦＧＦ、ＰＤＧＦ、ＥＧＦ、ＶＥＧＦ、ミッドカインケモカイン、レプチン、アンジオポエチンおよび他の成長因子、炎症性血管形成重合体または重合体構築物、電気活性重合体または他の微小傷害性重合体または局所刺激性重合体が挙げられる。好ましい細胞には、内皮細胞、ＥＣ骨髄前駆体細胞、他の幹細胞平滑筋細胞または前駆体、組合せ、神経細胞または神経幹細胞、あるいは上記との組合せが挙げられる。これらは、例えば、血管形成、筋形成または心筋組織修復に使用され、ここで、心筋には、重合体付加物またはマトリックスタンパク質混合物と共にまたはそれなしで、あるいは神経細胞または他のアドレナリン活性またはコリン活性細胞型と共に、筋細胞前駆体、分化型、同種移植片、同系移植片、異系移植片または異種移植片が配置される。新組織を電気的に駆動するか、鼓動させるか、衝撃を与えるか、または感知する手段（ハードワイヤまたは重合体）もまた、含まれ得る。

【００７８】

本質的に同じ技術が、神経細胞、シュワン細胞、星状細胞、グリア細胞および／または血管形成前駆体の移植による神経の再生または組織の再神経支配に使用され得る。１実施形態では、神経細胞は、重合体マトリックスと共に投与され、これらは、生体活性重合体、生体分解性生体安定性重合体（例えば、ポリエチレングリコール重合体、ヒアルロン酸およびラミニン）を含むかこれらから形成され得る。

【００７９】

さらに他の実施形態では、これらの技術は、ストレス応答誘発剤または真性ストレス（ａｃｔｕａｌ　ｓｔｒｅｓｓ）応答タンパク質を局所壁内送達するのに使用される。熱ショックタンパク質の発現を誘発するには、物理的刺激および化学的刺激の両方が使用され得る。最も頻繁に研究された刺激には、熱、酸化剤および重金属がある。あるいは、またはそれに加えて、熱ショックタンパク質は、処理する細胞に直接投与され得る。傷害に対する応答と相関すると考えられているものには、ｈｓｐ７０、ｈｓｐ９０および他の細胞質熱ショックタンパク質が挙げられる。これらのタンパク質のレベルを測定するアッセイは、当業者に周知である。しかしながら、熱ショックタンパク質の誘発は、有益な効果が得られる実際の機構ではあり得ず、所望の有益な効果を生じる適当な条件が使用されたことの指標にすぎない。

【００８０】

熱ショックタンパク質のいくつかの概説が公開されており、これには、Ｓｃｈｌｅｓｉｎｇｅｒ，Ｈｅａｔ　Ｓｈｏｃｋ：ｆｒｏｍ　ｂａｃｔｅｒｉａｌ　ｔｏ　ｍａｎ（Ｃｏｌｄ　Ｓｐｒｉｎｇ　Ｈａｒｂｏｒ，Ｃｏｌｄ　Ｓｐｒｉｎｇ　Ｈａｒｂｏｒ，ＮＹ　１９８２）；Ｌｉｎｄｑｕｉｓｔ，Ａｎｎ．Ｒｅｖ．Ｂｉｏｃｈｅｍ．５５：１１５１～１１９１（１９８６）；Ｐｅｌｈａｍ，Ｈ．Ｒ．Ｂ．，Ｃｅｌｌ　４６，９５９－６１（１９８６）；ＬｉｎｄｑｕｉｓｔおよびＣｒａｉｇ，「Ｔｈｅ　ｈｅａｔ－ｓｈｏｃｋ　ｐｒｏｔｅｉｎｓ」，Ａｎｎｕ．Ｒｅｖ．Ｇｅｎｅｔ．２２：６３１～６７７（１９８８）；Ｐｅｌｈａｍ，ＥＭＢＯ　Ｊ．８：３１７１～３１７６（１９８９）；Ｓｃｈｌｅｓｉｎ

ｇｅｒ Ｊ．Ｂｉｏｌ．Ｃｈｅｍ．２６５：１２１１１～１２１１４（１９９０）；Ｋａｕｆｍａｎｎ，Ｉｍｍｕｎｏｌ．Ｔｏｄａｙ １１：１２９～１３７（１９９０）；Ｍｏｒｉｍｏｔｏ Ｃａｎｃｅｒ Ｃｅｌｌｓ ３：２９５～３０１（１９９１）；Ｎｏｖｅｒ，「ＨＳＦｓ ａｎｄ ＨＳＰｓ － ａ ｓｔｒｅｓｓｆｕｌ ｐｒｏｇｒａｍ ｏｎ ｔｒａｎｓｃｒｉｐｔｉｏｎ ｆａｃｔｏｒｓ ａｎｄ ｃｈａｐｅｒｏｎｅｓ」，Ｓｔｒｅｓｓ Ｐｒｏｔｅｉｎｓ，ａｎｄ ｔｈｅ Ｈｅａｔ Ｓｈｏｃｋ Ｒｅｓｐｏｎｓｅ，Ｃｏｌｄ Ｓｐｒｉｎｇ Ｈａｒｂｏｒ Ｌａｂｏｒａｔｏｒｙ提供（Ｃｏｌｄ Ｓｐｒｉｎｇ Ｈａｒｂｏｒ，ＮＹ ＵＳＡ １９９１年４月２９日～５月２日） Ｎａｔｕｒｅ Ｎｅｗ Ｂｉｏｌ．３：８５５～８５９（１９９１）；ならびにＮｏｖｅｒおよびＳｃｈｅｒｆ「Ｈｅａｔ ｓｈｏｃｋ ｐｒｏｔｅｉｎ，ｉｎ Ｈｅａｔ Ｓｈｏｃｋ Ｒｅｓｐｏｎｓｅ（ＣＲＣ Ｐｒｅｓｓ，１９９１）４１～１２７ページが挙げられる。

【００８１】

殆どの場合、この生体活性剤は、組織表面または内腔内への適用および重合または固化の前に、その材料と混合することにより、物理的に取り込むことが可能である。この材料は、そのモノマー溶液中に混合されて、溶液、懸濁液または分散液が形成できる。他の実施形態では、この生体活性剤は、送達装置（例えば、マイクロスフェア、マイクロカプセル、リポソーム、細胞ゴーストまたは偽ビオリン）内にカプセル化され得、これらは、それ自体、細胞（例えば、食細胞）による放出速度および取り込みに影響を与える。

【００８２】

生体活性剤は、重合前または重合時に、この高分子材料に化学的に連結（共役）され得る。生体活性物質はまた、カテーテル、トロカール、内視鏡、ステントまたは組織シールまたはプラグまたは感知移植片（これらは、単独でかまたは高分子材料と組み合わせて、本明細書中に記載の処置に使用される）の表面に適用できる。カテーテルおよび他の装置または移植片本体は、標準材料（これには、外科用スチールのような金属、および熱可塑性重合体が挙げられる）から作製される。閉塞バルーンは、従順な材料（例えば、ラテックスまたはシリコーン）または非従順材料（例えば、ポリエチレンテレフタレート（ＰＥＴ））から作製され得る。この膨張可能部材は、好ましくは、非従順材料（例えば、ＰＥＴ、（ＰＶＣ）、ポリエチレンまたはナイロン）から作製される。そのバルーンカテーテル部分は、その重合体被覆の分離を助けるために、必要に応じて、シリコーン、ポリテトラフルオロエチレン（ＰＴＦＥ）のような材料、水和ヒドロゲルのような親水性材料および他の潤滑性材料で被覆され得る。シールおよびプラグは、上で挙げた構造的に生体分解性または生体安定性重合体から作製されるか、インサイチュで重合され、エキソビボで重合され、そして局所的に輸送されたヒドロゲルから作製されるか、あるいは乾燥（ｄｅｓｓｉｃａｔｅｄ）ヒドロゲルまたはオルガノゲルまたは上記混合物から作製され得る。感知／遠隔測定移植片（ｓｅｍｓｉｎｇ／ｔｅｌｅｍｅｔｒｉｎｇ ｉｍｐｌａｎｔ）は、重合体と、ミクロ電子工学装置、マイクロチップ、ＭＥＭＳまたは他の半導体型成分との組合せから作製され得る。

【００８３】

いくつかの生体適合性高分子材料は、表面変性の影響を受け易く、ここで、表面に結合した生体活性分子／リガンドは、細胞結合特性を示す。これらの方法は、Ｂｉｏｍａｔｅｒｉａｌｓ １０，１１～１５（１９８９）においてＴａｙ，Ｍｅｒｒｉｌｌ，Ｓａｌｚｍａｎ、およびＬｉｎｄｏｎにより記述されている。無水物または酸ハロゲン化物形態のＮ－保護アミノ酸、ポリ（アミノ酸）（２個～１０個のアミノ酸）、ペプチド（１０個より多く１００個までのアミノ酸）またはタンパク質と、重合体上の水酸基、チオール基またはアミン基とを反応させることにより、共有結合が形成され得る。このアミノ酸またはペプチド上のアミン基は、自己縮合を防止するために、この酸ハロゲン化物または無水物を形成する前に、保護しなければならない。Ｎ－保護は、当業者に周知であり、種々の保護基（例えば、カルボベンゾキシ（ＣＢＺ）基）を使用することにより、達成され得る。本明細書中で使用する「保護基」との用語は、官能基が反応するのを阻止する部分であって

、これは、この官能基を保護する必要がなくなったとき、開裂可能である。官能基の例には、アミノ基、水酸基、チオ基およびカルボキシレート基が挙げられるが、これらに限定されない。保護基の例は、当業者に周知である。カルボキシル含有化合物は、種々の官能基（例えば、水酸基、チオ基およびアミノ基）を含有し得、これらは、酸ハロゲン化物または無水物と反応し得る。これらの官能基は、自己縮合を避けるために、酸塩化物または無水物を形成する前に、保護されなければならない。この酸塩化物または無水物を形成し、引き続いて、他の分子上の水酸基、チオール基またはアミノ基と反応した後、この保護基は、「脱保護」工程で除去され得る。これらのＮ－保護アミノ基は、当業者に公知の手段により、脱保護され得る。これらの化合物上の任意の水酸基またはチオ基は、これらの酸ハロゲン化物または無水物と反応しないように、保護されなければならない。アルコールに適当な保護基の例には、トリアルキルシリル基、ベンジルエーテルおよびテトラヒドロピラニルエーテルが挙げられるが、これらに限定されない。これらの基は、当業者に公知の手段により保護され得、引き続いて、このエステル化が完了した後、脱保護され得る。保護基の例は、本明細書により参考として援用される、Ｇｒｅｅｎｅ，Ｔ．Ｗ．，およびＷｕｔｓ．，Ｐ；Ｇ．Ｍ．，「Ｐｒｏｔｅｃｔｉｖｅ Ｇｒｏｕｐｓ ｉｎ Ｏｒｇａｎｉｃ Ｓｙｎｔｈｅｓｉｓ」、第２版、Ｊｏｈｎ Ｗｉｌｅｙ ＆ Ｓｏｎｓ，Ｉｎｃ．，３１７～３１８頁（１９９１）に見出され得る。酸ハロゲン化物誘導体を調製する方法は、好ましくは、触媒量のＤＭＦと共に、ベンゼンまたはトルエン中で、カルボン酸を塩化チオニルと反応させることである。無水物を生成する公知の方法は、カルボン酸と無水酢酸とを反応させることである。この反応において、酢酸が形成されると、反応容器から留出される。ペプチドは、例えば、そのペプチド上のアミノ官能基を保護し、その重合体の酸部分の酸ハロゲン化物または無水物を形成し、この酸ハロゲン化物または無水物をその重合体上の遊離水酸基、チオール基またはアミン基と反応させ、次いで、そのペプチド上のアミン基を脱保護して、エステル化、チオエステル化またはアミド化を介してそこにペプチドが結合した重合体を得ることにより、その高分子材料に共有結合され得る（この高分子材料がアルファヒドロキシ酸（例えば、ポリ（乳酸））の重合体である場合）。このペプチドはまた、ジアルデヒド（例えば、グルタルアルデヒド）との還元的アミノ化を使用して、遊離アミンを介して、この重合体に結合され得る。ポリエステル表面上のエステル基は、加水分解され得、活性な水酸基およびカルボキシル基が得られる。これらの基は、生体活性分子と連結するのに使用され得る。好ましくは、その活性カルボキシレート基を酸ハロゲン化物形態または無水物形態に変換する前に、その活性水酸基は、得られる酸ハロゲン化物または無水物との反応を避けるために保護される。非限定的な例として、この活性水酸基は、ベンジルエーテルとして保護され得る。この活性水酸基は、次いで、この酸ハロゲン化物または無水物に変換され得、そして第二化合物上の水酸基またはアミノ基と反応して、エステル結合またはアミド結合が形成される。このＯ－保護水酸基は、次いで、脱保護され得る。

【００８４】

カップリング剤（例えば、カルボジイミド、ジイソシアネートまたはオルガノシラン）が生体活性剤に重合体または金属とセラミックスとを共有結合するには、使用できる。例えば、金属ステントは、アミノトリアルコキシシランの水溶液で処理され得る。これらは、アミノ官能性表面を形成し、これは、耐久性のある結合または制御された放出のために、カルボキシ官能性タンパク質と反応し得る。カルボジイミドは、カルボキシ官能基と反応し、アミノ反応性中間体を生成し得る。カルボキシ官能性重合体は、Ｎ－ヒドロキシスクシンイミドエステルを形成するように反応し得、これらは、ペプチド上のアミノ基と高い反応性を有する。この化学反応は、外科用封止剤であるＰＥＧ－ジ－Ｎ－ヒドロキシスクシンイミドおよびアルブミン（Ｂａｒｒｏｗｓら、３Ｍ Ｃｏｒｐｏｒａｔｉｏｎ）を形成するのに使用されるが、生体活性分子を重合体にカップリングするのに使用され得る。

【００８５】

（２．高分子材料の適用）

大まかに言えば、この高分子材料は、生体適合性高分子材料であり、これは、上記のよう

に、刺激または機械的圧力に応答して、種々の程度の流動性を有する。この材料は、その被覆プロセスが完了すると、インビボで、実質的に非流動性であるようにされる。この材料は、その流動形態または適合形態で、被覆する組織または装置表面と接触して位置付けられ、次いで、上記のように、それを非流動性または適合性にするように、刺激される。この高分子材料は、上記装置または当業者に公知の装置を使用して、それを適用する組織表面または装置に依存して、カテーテル、注射器または噴霧を使用して、内腔または壁内に適用される。

【００８６】

この被覆は、典型的には、ある型のカテーテル、トロカールまたはスコープを使用して、組織表面（例えば、動脈、尿道、脳または心筋の媒体）に適用される。その被覆材料は、好ましくは、１本の管腔または複数の管腔を備えた単一カテーテルまたは類似の装置を使用して、適用される。このカテーテルは、比較的小さい断面積でなければならない。臓器領域の内部へのアクセスを提供には、長く薄い管状カテーテル（これは、内視鏡による手引きを使用して操作される）が好ましい。あるいは、この装置は、光ファイバーまたは実先端カメラ（ＣＣＤ、Ｃ－ＭＯＳなど）によって、またはエコー感知、ＵＳ感知またはＧＰＳ位置決めシステムによって、直接的視覚化性能を有し得る。

【００８７】

この被覆材料の適用は、カテーテルを通って、モノマー、重合体、マクロマーまたはそれらの組合せの溶液、分散液または懸濁液を押し出して、組織の表面または内腔を被覆するか満たし、次いで、その流動材料と共に、架橋剤、ゲル化剤または架橋触媒を導入することによって、その被覆の形成を制御し、次いで、架橋および／またはゲル化が起こるような状態を変えることにより、達成され得る。それゆえ、バルーンカテーテルを使用するとき、そのバルーン内に加熱流体または冷却流体を流すと、その局所温度は、ゲル化または架橋が誘発されて材料を非流動性にするレベルまで変化し得る。局在化した加熱または冷却は、その処理部位上に加熱液または冷却液の流れを直接供給することにより、増強され得る。しかしながら、このバルーンを通ってまたはその中への流体流れを使用して、または温度制御流体がバルーンを通って管腔に入るように、部分的に穿孔したバルーンを使用して、熱的制御もまた、提供され得る。熱的制御はまた、抵抗加熱素子と接触し、そのカテーテル本体に沿って延びるワイヤを経由して、電気抵抗加熱を使用して提供され得る。この型の加熱素子は、ＤＣまたは高周波（ＲＦ）電流または外部ＲＦまたはマイクロ波照射を利用し得る。温度制御を達成する他の方法もまた使用され得、これには、内部光ファイバー（裸またはレンズ付き）を使用する光誘発加熱が挙げられる。あるいは、内蔵式流体流れシステム（これは、このバルーン、アクチュエータまたは表面の他の材料適用先端への流体の流入および流出を可能にする）は、重合体の流れ、溶融、設定および冷却および固定化を制御し得る。この重合体の調合物は、光を熱エネルギーに変換する成分を含有し得る。光、超音波または放射線を適用するために、類似の装置が使用され得る。

【００８８】

あるいは、これらの重合体は、種々の形状（例えば、ロッド、球体、折り畳んだシート、ヤーン、メッシュ、撚り糸、ロープ、粒子、非晶質形態、フレークなど）の固形材料として送達され得る。類似のヒドロゲル材料は、水和した形態、部分的に水和した形態または乾燥した形態の上記物理的外形で送達され得る。さらに規定したヒドロゲル形状（例えば、スパイク、灯心または他の路＋空隙形態を備えた球体）は、空隙を封止するか塞ぐか修復する目的のために、送達され得る。

【００８９】

前述の材料のいずれかは、それらの生理学的な適合性を改善するために、他の材料と混合され得る。これらの材料には、その材料を適用する特定の組織に依存して、緩衝液、生理学的な塩、通常の増粘剤または粘度改良剤、充填剤（例えば、シリカおよびセルロース誘導体）、および類似の機能を有する他の公知の添加剤が挙げられる。

【００９０】

この高分子材料の形態を固定する方法は、その初期高分子材料の特性に依存して、いくつ

かの様式で達成され得る。例えば、部分的に重合した材料は、バルーンを使用して膨張され得、その後、それらの状態は、例えば、その局所温度を高めるか光ファイバーを介してＵＶまたは可視光線を供給することにより、重合が完結できるように調節される。完全に重合したスリーブを軟化して、膨張および容易な再構成および局所成形を可能にするために、温度の上昇もまた使用され得、その後、熱源を取り除いたとき、それは、膨張位置で「固まる」。もちろん、この重合体スリーブがプラスチック材料であり、伸展すると永久的に変形するなら（例えば、ポリエチレン、ポリエチレンテレフタレート、ナイロンまたはポリ塩化ビニル）、特別な固定手順は、必要ではない。

【００９１】

本発明は、以下の非限定的な実施例を参照して、さらに理解できる。

【実施例】

【００９２】

（実施例１：内腔への組織接着剤の適用）

臓器に切開部を形成する。次いで、この内腔に、組織接着剤を適用して、創傷の治癒を高める。以下は、空隙を閉じるのに有用な組織接着剤の例である。

【００９３】

ａ．この内腔の部位で、１ｇｍの５０ｍｇフィブリノーゲン／ｍｌを、０．３ｇの１５０ＮＩＨ　Ｕトロンビン／ｍｌ（これは、１００ｍＭの$CaCl_2$を含有する）とインサイチュで混合する。これは、９０秒以内に、組織接着剤を形成する。

【００９４】

ｂ．この内腔の部位で、２ｇｍの１００ｍｇフィブリノーゲン／ｍｌを、０．３ｇの１５０ＮＩＨ　Ｕトロンビン／ｍｌ（これは、１００ｍＭの$CaCl_2$を含有する）とインサイチュで混合する。これは、３０秒以内に、組織接着剤を形成する。

【００９５】

ｃ．１ｇｍの５０ｍｇフィブリノーゲン／ｍｌに、１２．５ｍｇのε－アミノカプロン酸／ｍｌと共に、２５００ｋＩＵアプロチンニン／ｍｌを補充する。この溶液を、この内腔の部位で、０．３ｇの１５０ＮＩＨ　Ｕトロンビン／ｍｌ（これは、１００ｍＭの$CaCl_2$を含有する）とインサイチュで混合する。これにより、フィブリン接着剤のインビボ分解が遅くなり、長時間にわたって、内腔の崩壊状態が保持される。組織の良好な治癒応答のために、アプロチニンに代えて、トラネキサム酸が使用され得る。

【００９６】

（実施例２：接着剤の適用前の組織の脱水）

他の例では、濃縮したエタノール溶液（水中で、８０％ｗ／ｗ）で洗浄することに続いて、内腔を吸引する。このプロセスにより、この空洞の局所領域を脱水する。上記のように、インサイチュでフィブリン接着剤を適用して、組織の良好な接着性を増進する。

【００９７】

上記方法および組成物の改良および変更は、当業者に明らかであり、上記請求の範囲に含まれると解釈される。

【図面の簡単な説明】

【００９８】

【図１】図１は、壁内ゾーンにアクセスする以下の種々の手段を示す患者の略図である：洞内、包膜内、経皮、経胸郭、経皮経腹腔、経皮－開放、経動脈、経静脈、経リンパ腺、皮下および手術。

【図２】図２Ａ～２Ｇは、以下のためにカテーテル（これは、レザバおよび制御手段を含む）を使用した生体活性物質の導入を示す略図である：臓器にアクセスする（Ａ）（ここで、このカテーテルは、位置付けられ、安定化される（Ｂ））；管腔内ゾーンに貫入する（Ｃ）；壁内ゾーンに安定化する（Ｄ）（これは、必要に応じて、機械的、熱的、レーザー、高周波、紫外線、Ｘ線、電磁、音響または化学的手段を使用して、組織を除去する工程（Ｅ）を包含する）；生体活性剤（これは、薬理剤、細胞または生体物質を含有する）を送達する（Ｇ）；およびゾーンおよびアクセス路を封止する（Ｈ）。

【図３】図３Ａおよび３Ｂは、壁内ゾーン（図３Ｂ）に薬剤粒子（図３Ａ）を送達する膨張手段を含むカテーテルである。
【図４】図４Ａおよび４Ｂは、壁内ゾーン（図４Ａ）に薬剤粒子を送達する膨張手段を含むカテーテルおよびアクチュエータ手段（図４Ｂ）の拡大図である。
【図５】図５Ａおよび５Ｂは、圧電ポンプ（図５ａ）を含むカテーテルであり、ここで、このカテーテルは、さらに、壁内組織に薬剤粒子を分配する噴霧ノズル、案内手段、および流体または重合体用のレザバ、および重合体を融解する任意の加熱素子を含む。

【図１】

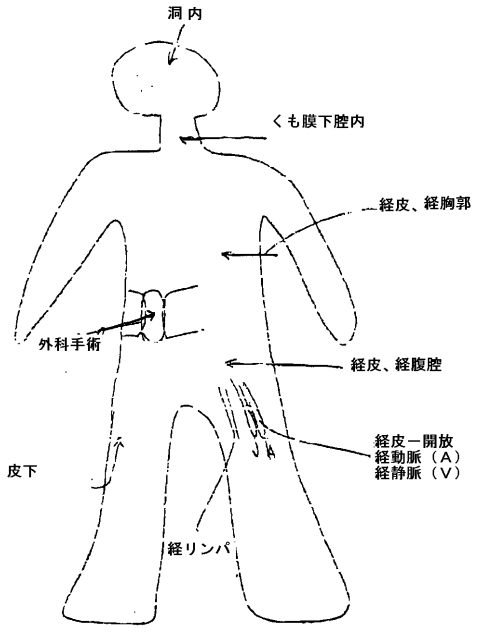
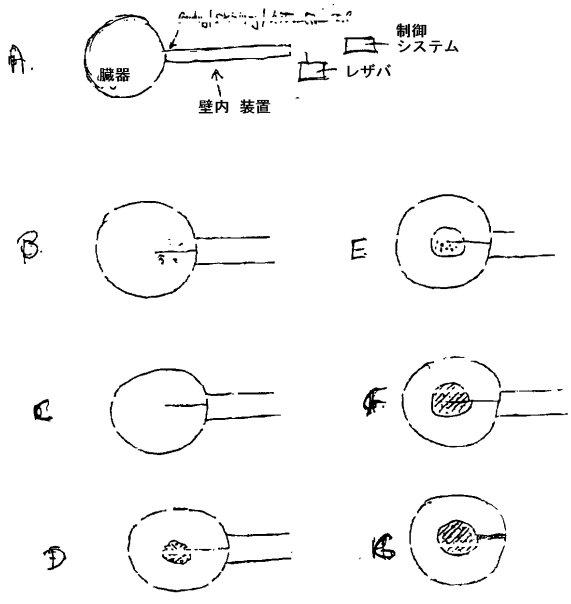


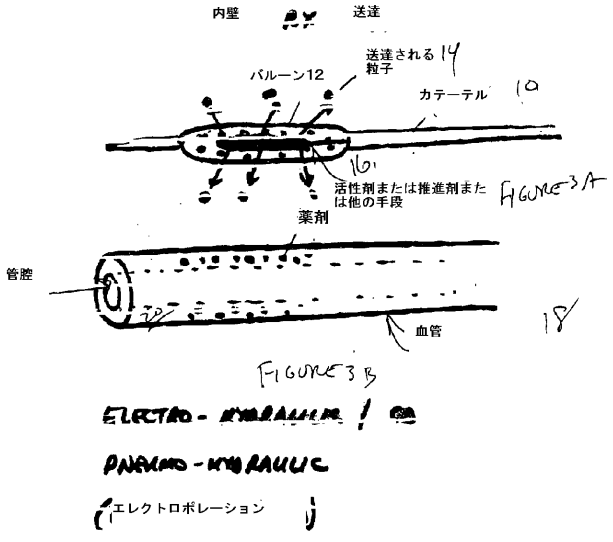
FIGURE 1

【図２】

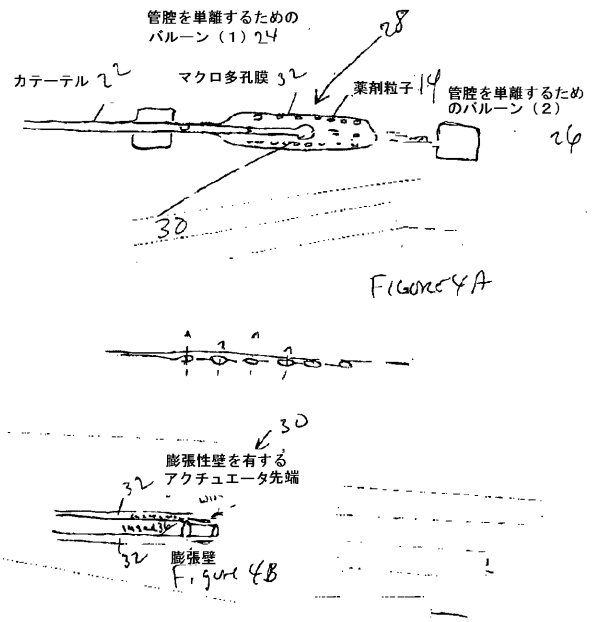


Figures 2A-G

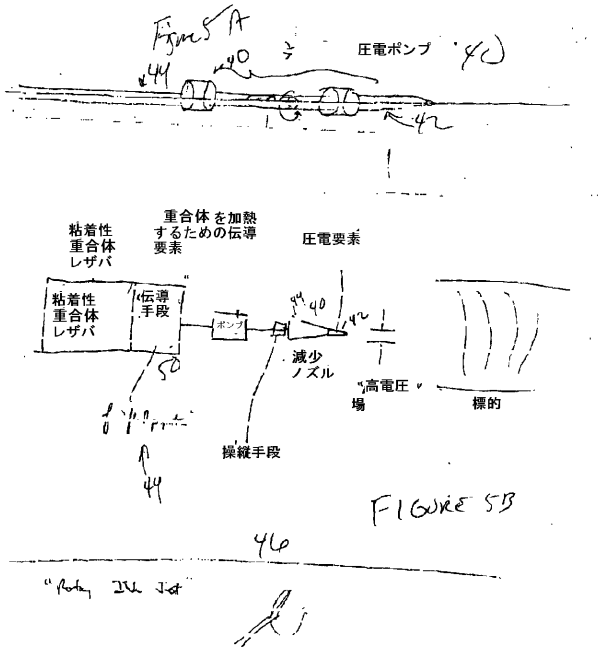
【図３】


内壁
送達
送達される粒子
バルーン12
カテーテル
活性剤または推進剤または他の手段
薬剤
管腔
血管
FIGURE 3A
FIGURE 3B
ELECTRO-
PNEUMO-HYDRAULIC
(エレクトロポレーション

【図４】


管腔を単離するためのバルーン（1）
カテーテル
マクロ多孔膜
薬剤粒子
管腔を単離するためのバルーン（2）
FIGURE 4A
膨張性壁を有するアクチュエータ先端
膨張壁
FIGURE 4B

【図５】


圧電ポンプ
粘着性重合体レザバ
重合体を加熱するための伝導要素
圧電要素
伝導手段
ポンプ
減少ノズル
高電圧場
標的
操縦手段
FIGURE 5A
FIGURE 5B

【国際公開パンフレット】

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 August 2002 (22.08.2002)

PCT

(10) International Publication Number
WO 02/064014 A2

(51) International Patent Classification[7]: A61B

(21) International Application Number: PCT/US02/03726

(22) International Filing Date: 8 February 2002 (08.02.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/267,578 9 February 2001 (09.02.2001) US

(71) Applicant: ENDOLUMINAL THERAPEUTICS, INC. [US/US]; 5001 North Summit Ridge Road, Tucson, AZ 85750 (US).

(72) Inventor: SLEPIAN, Marvin, J.; 5001 North Summit Ridge Road, Tucson, AZ 85750 (US).

(74) Agents: PABST, Patrea, L. et al.; Holland & Knight LLP, One Atlantic Center, Suite 2000, 1201 West Peachtree Street, N.E., Atlanta, GA 30309-3400 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/064014 A2

(54) Title: ENDOMURAL THERAPY

(57) Abstract: Methods, devices and materials for the treatment or repair, replacement, transplantation or augmentation of tissues in endomural zones specifically by open surgical, minimally invasive or percutaneous transmural or trans parenchymal application of polymeric material alone or in combination with bioactive agents or cells, have been developed. These methods and systems are useful to repair, after function, replace function or augment function of the central or endomural aspects of solid organs or tubular body structures.

ENDOMURAL THERAPY

Background of the Invention

This invention relates to an aspect of *in situ* tissue engineering of organs or organ components, and repair, replacement, or alteration of function via manipulations targeted to the middle or endomural aspects of tissues.

This application claims priority to U.S.S.N. 60/267,578 filed February 9, 2001.

This invention relates to devices, materials and methods for the treatment or repair of tissues, specifically by accessing the endomural zone (middle zone) of organs, organ components or tissues, either via surgical or percutaneous application of devices, polymeric materials, alone or in combination with bioactive agents or cells.

Many diseases involve the central aspects of organs, e.g. tumors in the liver, atherosclerotic lesions within the walls of arteries, adenomas in the prostate, malignancies within the brain, etc. Today the majority of these types of lesions are removed via open surgical, minimally invasive or percutaneous procedures which make direct incisions into the organ beginning on the ectoluminal or endoluminal surface. As such these approaches remove much healthy tissue in surrounding unaffected tissue layers, in the process of removing or treating the diseased zone. For example, in open surgical removal of an intra-organ tumor the capsule and ectoluminal zones as well as surrounding endomural healthy zones are often violated and excised in the process of removing the contained disease zone. While this therapy is effective it has the added morbidity burden of "mass" rather than "selective" destruction or treatment.

The same issue of unnecessary tissue damage and removal holds true for percutaneous or endoluminally accessed and treated disease. Access to the endoluminal regions via this route has traditionally removed the overlying endoluminal layers and surrounding endomural healthy zones to get at diseased zones within. An example of this may be seen in the current therapy for

prostatic adenomas, the TURP (Transuretheral resection of the Prostate) procedure. In TURP the normal urothelial mucosal layer is removed as well as the peri-urethral column to gain access and remove intra-organ contained adenomas. This approach, while effective in removing the contained disease zone, unfortunately removes a significant amount of normal non-diseased tissue at the same time. As such, current procedures carry unnecessary morbidity and mortality due to their invasiveness and associated trauma.

Another limitation of current therapies lies in the fact that many diseases involve cellular derangement in the endomural zones while current therapies often only treat outer, either endoluminal or ectoluminal, zones. An example of this may be seen in therapy of atherosclertic lesions of coronary and peripheral arteries. In cases of severe atherosclerotic obstruction, endovascular removal of obstructive lesions via endovascular atherectomy, a catheter-based shaving, coring or drilling procedure from within the vessel is often employed. These approaches remove the diseased atheroma close to the vessel lumen and close to the treatment device. However, they do not tackle the source or "core' of the disease which frequently lies in the media of the artery, the endomural zone of the vessel.

Many therapies today are administered systemically with the goal of achieving a local intra-organ effect. If systems and methods existed which would provide mechanical physical targeting with simultaneous sustained intra-organ presence more effective, more accurate, site specific therapies would be achieved. Many "local" therapies are not local but regional and in fact affect adjacent zones. An example of this is intra-arterial chemotherapy for intra-hepatic malignancy such as hepatoma or hepatic metastasis. In this therapy drugs are adminstered via the hepatic arterial or vasculature system to treat disease within the organ but in fact the entire organ from within and without is bathed with medication. Further hepatically delivered medication subsequently diffuses or mixes directly intralumenally with systemic blood.

It is therefore an object of the present invention to provide methods and devices for treatment of diseased organs or tissues with minimal damage to surrounding tissue.

It is a further object of the present invention to provide methods and devices for treatment of cental, core or generally "endomural" zones of diseased organs or tissues with minimal damage to surrounding tissue

It is a further object of the present invention to provide methods and devices for treatment of specific tissues while avoiding systemic toxicity.

It is a further object of the present invention to provide polymeric materials, drugs and biologically active compositions which can be delivered or released endomurally to aid in healing.

It is a still further object of the present invention to provide devices, both surgical and percutaneous to access and modify endomural tissues and/or deliver polymeric materials, drugs and biologically active compositions which can be delivered or released endomurally to aid in healing.

Summary of the Invention

Methods, devices and materials for the treatment or repair, replacement, transplantation or augmentation of tissues in endomural zones specifically by open surgical, minimally invasive or percutaneous transmural or trans parenchymal application of polymeric material alone or in combination with bioactive agents or cells, have been developed. These methods and systems are useful to repair, alter function, replace function or augment function of the central or endomural aspects of solid organs or tubular body structures.

Brief Description of the Drawings

Figure 1 is a diagram of a patient showing the various means of accessing the endomural zones: intra sinus, intrathecal, percutaneous transthoracic, percutaneous transabdominal, percutaneous - open, transarterial, transvenous, translymphatic, subcutaneous, and surgical.

Figures 2A-G are diagrams showing introduction of bioactive material using a catheter including a reservoir and control means to access the organ (A),

where the catheter is positioned and stabilized (B), the endoluminal zone penetrated (C), stabilized in the endomural zone (D), optionally further including the step of removing tissue, using mechanical, laser, thermal, radiofrequency, ultraviolet, x-ray, electromagnetic, acoustic or chemical means (E), delivering biologically active agents, including pharamcologic agents, cells, or biomaterials (G), and sealing the zone and access tract (H).

Figures 3A and 3B a catheter including expansive means for delivery of drug particles (Figure 3A) into the endomural zone (Figure 3B).

Figures 4A and 4B are a catheter including an actuator means for expanding expansive means for delivery of drug particles into the endomural zone (Figure 4A) and an expanded view of the actuator means (Figure 4B).

Figures 5A and 5B are a catheter including a piezoelectric pump (Figure 5a), where the catheter further includes a spray nozzle for dispensing drug particles into endomural tissue, guide means, and a reservoir for fluids or polymer and an optional heating element for melting of the polymer.

Detailed Description of the Invention

A method has been developed for treatment of endomural tissue. The method generally include placing a tubular tissue accessing device (needle, trocar, catheter) percutaneously into the organ. Tissue is removed in the organ. A flowable preformed or dessicated hydrogel or solid polymer plug is placed into the hole, filling the void and sealing the tissue tract. This method is useful in a variety of applications. For example, the endocardial (or epicardial) surface is accessesed via delivery device, the device is stabilized against the heart wall, the myocardium is penetrated to access the endomural zones, a space or void is created, and cells, polymers,drugs and genes or combination of these in varying sequences can delivered to the myocardium. The void mass or plug is then sealed in place.

This method is generally shown in Figure 1 and Figures 2A-2G. The method includes the steps of:

1. Access close to organ, either percutaneously, surgically, laparoscopically, transvacularly, transenterally, intrathecally, subcutaneously via tissue planes, translyphatically,etc.

2. Park and stabilize in location the delivery means.

3. For endo or ecto access, penetrate endoluminal zone, stabilize in endomural zone, locally treat tissue, and remove tissue – mechanically, thermally, with laser, radiofrequency, ultraviolet, x-ray (any form of tissue damaging), electromagnetic energy, acoustic energy (ultrasound), dessication, gas exposure (CO_2, ether), chemically – antimetabolics, antineoplastic, anti-inflammatory, antimicrobial, antiviral, antibiotics, hormones, antibodies, etc.

4. Deliver agents, such as pharmacologic agents, cells, or other biologicals or biomaterials.

5. Seal zone and access tract .

Definitions

I. General Organization of Higher Animals:

The structural organization of higher animals such as mammals, including man, is that of multiple integrated and interactive tissue components. These tissues may be organized as discrete organs which are functional factories, e.g. liver producing biochemical mediators or device systems, e.g. heart – mechanically pumping blood and brain – electrically signaling and coordinating events. As referred to herein, organs include solid and hollow organs, e.g. the liver and colon, respectively.

Alternatively, animals contain tissue components which are largely conduits for functional fluids such as blood, lymph, endocrine or exocrine secretions or gases. These tubular "organ components" or conduits are structures such as arteries, veins, lymphatics, bile ducts, ureters, fallopian tubes, etc.

II. Structure of Organs and Organ Components – The Endomural Zone Defined

Discrete organs may be generically described as having three regions or zones. These regions include: 1. the ectoluminal or outer zone (i.e. capsule, serosa, etc.), 2. the endomural or middle zone and 3. the endoluminal zone. In discrete organs the ectoluminal region typically functions to protect and contain the organ. The endomural zone of the organ is typically the functional or "business end," of the organ, acting as a biochemical factory for production of homeostatic proteins, hormones, enzymes and immunoglobulins for defense and reparative cells for tissue repair, organ regeneration, , metabolism or other specialized functions. In mechano-dynamic organs such as the heart and lung, the endomural zones function to propel or exchange fluid or gas. The inner or ectoluminal zone of organs may have functions similar to the endomural zone or act as yet another internal boundary or barrier layer. If an organ is cut in cross-section the ectoluminal zone may be characterized as the outer 10% ± 10 cross-sectional area, the endomural zone as the mid 80% ± 10 and the endoluminal zone as the inner 10% ± 10.

In addition to solid or hollow organs with cavities true tubular organs and organ components exist as vital body structures. Examples of tubular organs include the small intestine and the colon. Tubular organ components include major interpenetrating blood vessels in organs, e.g. the portal vein in the liver, the cavernous sinus in the brain. Examples of tubular tissue structures, include ducts, e.g. the bile duct, or blood vessels, e.g., arteries or veins.

Tubular organs and tissue structures in general have a laminated, multi-layer "tube-in-tube' structure made of at least three layers. All of these tubular organs, organ components or tissue structures may be characterized in similar fashion as outlined for organs above into ectoluminal, endomural and endoluminal zones. In tubular structures the ectoluminal zone may be characterized as the outer 10% ± 10 cross-sectional area, the endomural zone as the mid 80% ± 10 and the endoluminal zone as the inner 10% ± 10. Interestingly, tubular organs and tissue structures have defined histologic layers which generally correlate with these zones. The ectoluminal zone correlates

with serosa or adventitia. The endoluminal zone correlates with the lamina propria, submucosa, muscularis, or media. The endoluminal zone correlates with the intima or mucosa.

Methods of Treatment

I. Localized Treatment

Methods which focus on treatment of the endomural region of an organ or tissue provide a means to reduce the trauma to adjacent, contiguous or "collateral," healthy tissue associated with removing, containing or locally treating active disease within central or endomural regions of an organ or tissue structure. This also allows the disease to be treated more effectively, on a local basis, with agents, cells or systems without risk of systemic exposure. Through local application of polymers, pharmaceuticals, genes, therapeutic peptides, cells, radiation systems, etc., one is able to focus therapy to the affected zone of an organ while sparing exposure of surrounding contiguous or adjacent healthy tissue. Local intra-organ therapy reduces systemic exposure to agents which may have deleterious effects systemically. This allows application of higher effective concentration of agents without fear of toxicities with reduced systemic spillover effects.

Endomural treatment also provides a means for sustained durable local therapy, as well as containment and hence sustained exposure or therapeutic presence in an organ compared with conventional parenteral or topical therapy, over longer periods of time than are typical with systemic delivery. Creating cavities or pockets within an organ allows "rebuilding" and reconstruction from inside. Placing therapeutic agents or materials in a "privileged zone," free from overlying blood flow, increases retention and thereby sustains action of the agents. This also provides for more accurate therapy.

Endomural treatment not only localizes the treatment modalities, but also cordons off disease physically, creating barriers to the disease as well as local treatment of the disease.

II. Use of Endomural regions of Organs as Seed Beds

Endomural therapy provides the potential to utilize one organ bed or body as a soil in which to place or plant cells, or organ components to provide another function normally provided by another organ. In many disease states a vital function of an organ is diminished or destroyed by a disease. Conventional therapy aims to pharmacologically limit resultant symptoms or attempt to restore lost function. These approaches are limited. Despite disease of the organ, the remaining tissue components or stroma often have relevant functions themselves. Further, even if specialized tissues and cells of a given organ are diseased, the vascular, neural and stromal matrix of the organ are often intact and are a functional generic organ bed. These residual structures may be looked upon as a fertile "soil" for transplantation or implantation of cells, cell-polymer combinations, other organ components, organoids, artificial organs or bioreactors. These diseased organ shells will function to provide a bed for engraftment of these implants with "housekeeping functions," i.e. arterial and venous supply, lymphatic drainage, innervation, etc., already built-in and intact.

III. Application of Polymeric Structural or Bioactive Materials

As noted above, therapeutic materials such as drugs and cells can be administered and contained intramurally, for treatment of a disease or to provide supplementary function. Other materials, for example, polymers having additional properties such as the ability to facilitate healing, minimize or provoke inflammation, decrease fibrotic response, inhibit abnormal proliferation or other therapeutic benefits, may also be utilized. Polymers may be themselves bioactive or contain embedded or grafted bioactive molecules, peptides, lipids, drugs or other moieties. These polymers may either suppress, maintain or stimulate a biological response. The polymers may also serve as tissue glues, adhesives or sealants to isolate tissue zones, creating internal barriers. These polymers may also serve to provide an artificial biodegradable or permanent scaffold or stroma for implanted or transplanted cells, fragments or tissues.

IV. How to access organ

An organ or tissue can be accessed surgically, either by open exposure or using minimally invasive techniques; or percutaneously.

The endomural regions of an organ or tissue can also be accessed surgically, through open exposure of internal organs or though trans-body wall incisions. This is typically followed by defined focused narrow puncture of the organ, without open radical dissection, and subsequent entry into the endomural zone and placement of a therapeutic.

Endoluminal entry is typically achieved via the use of needles, trocars, ballistic transfer – explosive bullet-like, spark projection, projectile pellets e.g. gene gun, pneumatic transfer (high pressure air, CO_2), chemical permeation, optical or other irradiation-based penetration, ultrasound, electroporation or pheresis –mediated transfer.

These routes and means of penetration are minimally invasive, may be used via direct tissue contact or through key-hole or other limited port entry into the inner aspects of the body, with subsequent defined focused contact and similar penetration means or through subsequent narrow or limited physical puncture of the organ, without open radical dissection, and subsequent entry into the endomural zone for placement of a therapeutic either directly or through the above limited penetration, permeation or other transport means.

Figures 3-5 demonstrate devices which may be used for this purpose. Figure 3A shows a simple balloon device, wherein the catheter 10 includes a balloon 12 permeable to the drug particles 14 to be delivered. An activating or propelling agent or other means 16 within the balloon 12 is used to propel the drug particles 14 out of the balloon 12 and into the tissue as shown in Figure 3B. Figure 3B shows a blood vessel 18 wherein the drug particles 14 have become embedded within the endomural zone 20.

In another embodiment shown in Figure 4A, drug particles 14 can be delivered to a desired location within the endomural zone by introducing a catheter 22 into the tissue lumen, wherein the catheter22 has two expansile members 24 and 26, typically balloons, and means 28 for delivering the drug

particles 14 at a space between the two members 24 and 26; expanding the expansile members 24 and 26 to occlude the targeted portion of the lumen, administering the drug particles 14 by administering a force via an actuator means 30 that propels the drug particles 14 through a macroporous membrane 32 and into the endomural zone, contracting the expansile members 24 and 26, and removing the catheter 22. In one preferred embodiment, the catheter is also used to wash out the occluded region so that, in the case of a blood vessel, the region is substantially free of blood. Figure 4B is an expanded view of the actuator means 30, with expandable walls 32, a tip 34 to insert the actuator means into the delivery means 28, and propellent means 36. The propellent means 36 can be an explosive, hydraulic, or other energy generating means.

As shown in Figure 5A, the drug particles can be delivered using other means, such as a piezoelectric pump 40. The pump 40 includes a nozzle 42 which is rotatable as well as capable of being angled to deliver drug to the appropriate target. This is attached to a catheter 44 including a proximal balloon, distal balloon, guide wire (or other steering means) 46, and, optionally, means 48 for dispersing one or more other materials (including washing or irrigation fluids, adhesive or polymer solutions), etc. and optionally conductive means for heating materials 50, as shown in Figure 5B.

Delivery can also be via a percutaneous route, for example, through transcutaneous entry into conduit systems or "highways" of the body. One advances to the desired region of interest under direct visual guidance, fluoroscopy or ultrasonic guidance, with subsequent entry into the endomural and/or endoluminal zones and placement of a therapeutic, as necessary as outlined above.

Implantable devices or delivery means can include sensors for data measurement, and/or data analyzers, and/or data storage means, and/or data telemetry/transmission means including means for communication at mutiple levels of isolated or nested levels of information transfer. These devices may have incorporated means for modification of the implant or mounting a

response, e.g. local or systemic drug delivery, in response to measurements made using the sensors. These are particularly useful in urology, hepatology or cardiology, where the implants contain one or more sensors responsive to variables which change over time, for example, pressure which is indicative of changes in fluid flow and diameter of the ureter, biliary duct or vessel in which the implant has been placed. Feedback from the sensor(s) either directly, or indirectly via monitoring means external to the patient, signal changes that may be required, such as expansion of the implant in the case where the tissue lumen diameter changes over time or the implant becomes unstable or migrates. In another embodiment, the implant contains a bioactive, prophylactic, diagnostic or pH modifying agent. In one embodiment, the implant is formed of a temperature or pH responsive material so that the agent is released when the temperature or pH is altered.

These systems can also be used to connect a patient to a remote data storage or manipulation system, such as a watch-like device, small portable device, intra or extradermal implant, phone system devices (portable phones, answering services, beepers, office fax machines), portable computer, personal digital assistant (PDA, e.g., Palm Pilot™ systems), or to the internet (world wide web) or a computer accessible through devices that the physician or nurse can monitor or use to interact remotely with the implant.

V. How to create repository zones in organ

Voids may be created via simple catheter, trochar or needle insertion. The void may be of identical size to the insertion device. Alternatively, the void may be made larger via expansile cutter systems which fan-out in a radial or conical or other geometric shape way. Voids may also be created via other mechanical means, e.g. tissue morcellator, balloon dilator, mechanical tissue jack or stretcher, thermal, electrical, ultrasonic laser, UV, x-ray, or other injurious or ablative electromagnetic radiation, cryogenic, chemical – e.g. acids. alkali, detergents, osmotic fragility means, or enzymatic means, e. g. papain, trypsin, chymotrypsin, matrix metalloproteinases, fibrolytic agents,

streptokinase, and tissue plasminogen activator. Aspiration, perfusion or superfusion may be used to further wash and expand the voids.

Voids may be filled with drugs, polymers, polymer-drug mixtures or covalently linked drug-polymer combinations. Polymers may be utilized to further facilitate void creation via delivery of void forming agents, to fill an initially created void for therapeutic purposes, to deliver subsequent therapeutic agents in a tiered or sequenced therapeutic scheme, to limit further void expansion, to provide a neomatrix or scaffold for subsequent cell or tissue engraftment or to form a void- or cavity-barrier limiting void entry or exit. Further, these barriers may be selectively permeable in either a unidirectional or bi-directional fashion.

Polymers may be therapeutic or serve as the means for delivering therapeutic agents. Polymers may be inserted in simple spaces created via device insertion or in larger spaces created as a result of initially creating tissue defects, voids or other cavities. Voids created as a result of disease, defect or surgical procedure are filled with adhesive polymers that facilitate void cavity wall bonding and healing. Polymers are specifically selected to minimize inflammation, secondary bleeding and late fibrotic scarring. Alternatively if an angiogenic or fibrogenic response is desired, polymers may be selected so as to induce a pro-inflammatory, angiogenic, fibrogenic response.

Tissue voids within an organ can be filled with biocompatible biodegradable polymers to act as intra-void tissue bonding agents, allowing collapse and exclusion of the void space while simultaneously increasing intramural lumen space. The polymers may either spontaneously solidify or they may be polymerized or bound to the tissue upon exposure to an appropriate stimulus, as discussed in more detail below. Polymer may posses "therapeutic' hygroscopic or hydrophobic properties to either facilitate progressive water uptake and void shrinkage or to prevent uptake allowing tissue swelling. The polymers are selected to facilitate healing, with minimal inflammatory and late fibrotic responses. Coordinating use of tissue friendly biodegradable polymeric

bioadhesives insures frank volume reduction and obliteration of cavities formed via direct tissue excision. Furthermore, the polymeric materials having drugs, genes or cells incorporated therein may serve as local depots for prolonged delivery of synergistic biochemical and cellular therapeutics, for example, to promote healing, decrease inflammation and/or collagen deposition and scarring, and manipulate endocrine processes and local growth control.

VI. How to implant in the organ

These materials can be implanted in the organ directly, in repository zones, created as described above. Materials to be implanted other than drugs and polymers include cells. Cells can be grown *in vitro*, in cell culture or obtained by biopsy. Cells may be genetically modified. Cells may be isogeneic, allogenic or xenogeneic. Allogenic or xenogeneic cells may be encapsulated for immunotolerance.

Cells may be added as single cells, slurries of single or multiple cell types or from multiple sources, organ fragments or tissue shards. Cells added to a given organ or organ component may be identical or similar differentiated normal cells, different differentiated normal cells, progenitor cells, genetically transfected, transformed or engineered cells, stem cells, embryonic cells, multipotential cells, primordial cells, allogeneic, heterogeneic, xenograft cells, encapsulated allogeneic, heterogeneic, or xenograft cells. Therapeutic non-mammalian, eukaryotic, plant or prokaryotic cells may be delivered.

Therapeutic biologicals such as cell fragments, heterokaryons, viruses, pseudovirions, viroids, prions, DNA, or RNA (sense, antisense, ribozymes or aptemers) may be co-delivered.

Plant cells, prokaryotic cells, or artificial cells may be administered as therapeutically indicated as well. These cells may be passivated or encapsulated to facilitate seeding and routing and to prevent immunorejection.

Cells or tissues from different organs may be transplanted from one organ to function as a substitute in another organ. For example, one could transplant splenocytes into a liver shell or scar or myocardial scar to act as

angiogenic precursors. One could transplant neural stem cells or dorsal root ganglion cells into the heart of patients with diabetes to return sensation of angina as a therapeutically beneficial return of a clinical warning sign. One could transplant splenocytes into bone marow to act as hematologic precursors.

VI. Polymeric or Hydrogel Materials

Biodegradable and/or biocompatible materials may be used to fill, shape, bulk or adhere to voids, cavities, channels or other spaces created by the endomural therapeutic devices to enhance healing, to provide structural support within the cavity, tubular organ or organ component a to assist or obviate the need for other lumen or cavity support following surgery, and/or for drug delivery. For example, polymeric or hydrogel materials can be applied at the surface of or interior of cavities created by removal of tissue to treat the disorders caused by overproliferation or inflammation of tissue. These materials can be used to adhere the sides of the tissue cavity together, to form a barrier at the surface of one or more of the tissue surfaces (to minimize inflammatory processes, for example), for delivery of bioactive agents, for the retention of radioisotopes, radioopaque particulate etc. The polymer may be deployed in the interior of the endomural tissue of the vessel or organ from the surface or tip of the catheter, as discussed above. Alternatively, the polymer can be applied by spraying, extruding or otherwise internally delivered via a long flexible tubular device consisting of as many lumens as a particular application may dictate.

Preferably, the method utilizes biodegradable or bioerodible synthetic or natural polymers, with specific degradation, lifespan and properties, which can be applied in custom designs, with varying thicknesses, lengths, and three-dimensional geometries (e.g. spot, stellate, linear, cylindrical, arcuate, spiral 8, etc.). The pharmaceutical delivery function of the process may be readily combined with the "customizable" deployment geometry capabilities to accommodate the interior of a myriad of complex organ or vessel surfaces. For example, polymer can be applied in either single or multiple polymer layer

configurations and different pharmacological agents can be administered by application in different polymer layers when multiple polymer layers are used.

1. Selection of Polymeric Materials

A variety of different materials can be used, depending on the purpose, for example, structural, adhesive, barrier, or drug delivery. For those applications where structure is required, a polymer is selected which has appropriate mechanical and physical properties. It is preferred that the polymer be biodegradable over a period of time required to heal and form the tissue as desired according to the application. This may be a few days, weeks, or months. An advantage of the polymeric materials is that they can be tailored to shape the polymer into uneven surface interstices, while maintaining a smooth surface with good flow or other tissue compatibility characteristics. Tissue narrowing, if it does occur, tends to stabilize beyond the six month window following the initial procedure without further accelerated narrowing. Optimally, if a foreign support device or sealant material is to be introduced into the tissue, it needs to exert its intended effect principally during the period of healing and peak inflammatory reaction. Although described herein principally with reference to polymeric materials, it is to be understood that other materials may also be used. For example, relatively low molecular weight organic compounds such as common sugars (e.g. sucrose), which are cast from concentrated, warm aqueous solution to set up as monolithic solids *in situ* and erode with minimal swelling or fragmentation may be used in place of a polymeric material. Inorganic compounds formed by ion exchange, such as polysilicic acid salts, degradable bioceramics, and "plasters" which degrade by surface erosion but which set *in situ* can also be used.

For those applications where the purpose does not require structural support properties, the polymer may be formed of a material that is bioadhesive, or impermeable to molecules of specified molecular weights, or highly permeable, releasing incorporating drug over a desired period of time, and consist of as little as a single layer of polymer.

Accordingly, the nature of the polymeric material used will be determined by whether it functions as a coating, bandage, adhesive, drug delivery device, or mechanical support role. Further, the choice of polymer must appropriately balance the degree of structural and geometric integrity needed against the appropriate rate of biodegradation over the time period targeted to prevent an undesirable reaction. In some cases, the material may be the same for different purposes where the ultimate *in vivo* geometry of the polymer dictates the final function of the polymer coating. The thinner applications allow the polymer film to function as a coating, sealant and/or partitioning barrier, bandage, and drug depot. Complex internal applications of thicker layers of polymer may actually provide increased structural support and, depending on the amount of polymer used in the layer, may actually serve in a mechanical role to maintain vessel or organ patency. For example, lesions of tissues that are comprised mostly of fibromuscular components have a high degree of visco-elastic recoil. These lesions or tissues require using the process to apply an endomural coating of greater thickness or stiffness and extent so as to impart more structural stability thereby resisting vessel radial compressive forces. This provides structural stability and is generally applicable for the maintenance of the intraluminal geometry of all tubular biological organs or substructure.

The basic requirements for the polymeric material are biocompatibility and the capacity to be applied in a solid or fluent state then chemically or physically reconfigured under conditions which can be achieved *in vivo* to yield a non-fluent polymeric material having defined characteristics in terms of mechanical strength, permeability, adhesion, and/or release of incorporated materials.

The polymeric materials can be applied as polymers, monomers, macromers or combinations thereof, maintained as solutions, suspensions, or dispersions, referred to herein jointly as "solutions" unless otherwise stated. Polymeric materials can be thermosettable, thermoplastic, polymerizable in response to free radical or ioin formation such as by photopolymerization,

chemically or ionically crosslinkable (i.e., through the use of agents such as glutaraldehyde or ions like calcium ions). Examples of means of solidifying or polymerizing the polymeric materials including application of exogenous means, for example, application of light, ultrasound, radiation, or chelation, alone or in the presence of added catalyst, or by endogenous means, for example, a change to physiological pH, diffusion of calcium ions (e.g., alginate) or borate ions (e.g., polyvinyl alcohol) into the polymeric material, or change in temperature to body temperature (37°C.).

Although either non-biodegradable or biodegradable materials can be used, biodegradable materials are preferred. As used herein, "biodegradable" is intended to describe materials that are broken down into smaller units by hydrolysis, oxidative cleavage or enzymatic action under in vivo conditions, over a period typically less than one year, more typically less than a few months or weeks. For application to tissues to prevent inflammation, enlargement and/or overproliferation, it is preferred to use polymers degrading substantially within six months after implantation. For prevention of adhesions or controlled release, the time over which degradation occurs should be correlated with the time required for healing, i.e., generally in excess of two weeks but less than six months.

Suitable materials are commercially available or readily synthesizable using methods known to those skilled in the art. These materials include: soluble and insoluble, biodegradable and nonbiodegradable natural or synthetic polymers. These can be hydrogels or thermoplastics, homopolymers, copolymers or blends, natural or synthetic. As used herein, a hydrogel is defined as an aqueous phase with an interlaced polymeric component, preferably with 90% of its weight as water. The following definition is from the Dictionary of Chemical Terms, 4th Ed., McGraw Hill (1989): Hydrogel: a colloid in which the disperse phase (colloid) has combined with the continuous phase (water) to produce a viscous jellylike product, for example, coagulated silicic acid. An organogel is defined as an organic phase with an interlaced polymeric

component, preferably with 90% of its weight as organic solvent. Preferred solvents include non-toxic organic solvents, such as dimethyl sulfoxide (DMSO), and mineral and vegetable oils. The preferred polymers are synthetic polymers, formable or synthesizable *in situ*, with controlled synthesis and degradation characteristics.

Representative natural polymers include proteins, such as zein, modified zein, casein, gelatin, gluten, serum albumin, or collagen, and polysaccharides, such as cellulose, dextrans, hyaluronic acid, polymers of acrylic and methacrylic esters and alginic acid. These are not preferred due to higher levels of variability in the characteristics of the final products, as well as in degradation following administration. Synthetically modified natural polymers include alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, and nitrocelluloses, acrylic or methacrylic esters of above natural polymers to introduce unsaturation into the biopolymers.

Representative synthetic polymers include polyesters, polyphosphazines, poly(vinyl alcohols), polyamides, polycarbonates, polyalkylenes, polyacrylamides, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polysiloxanes, polyurethanes and copolymers thereof. Other polymers include celluloses such as methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethyl cellulose, cellulose triacetate, cellulose sulfate sodium salt, acrylates such as poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), polyethylene, polypropylene, poly(ethylene glycol), poly(ethylene oxide), poly(vinyl acetate), polyvinyl chloride, polystyrene, polyvinyl pyrrolidone, and polyvinylphenol. Representative

bioerodible polymers include polylactides, polyglycolides and copolymers thereof, poly(hydroxy butyric acid), poly(hydroxyvaleric acid), poly(lactide-co-caprolactone), poly[lactide-co-glycolide], polyanhydrides, polyorthoesters, blends and copolymers thereof.

These polymers can be obtained from sources such as Sigma Chemical Co., St. Louis, MO., Polysciences, Warrenton, PA, Aldrich, Milwaukee, WI, Fluka, Ronkonkoma, NY, and BioRad, Richmond, CA. or else synthesized from monomers obtained from these suppliers using standard techniques.

These materials can be further categorized as follows.

Materials which polymerize or alter viscosity as a function of temperature.

Poly(oxyalkene) polymers and copolymers such as poly(ethylene oxide)-poly(propylene oxide) (PEO-PPO) copolymers, and copolymers and blends of these polymers with polymers such as poly(alpha-hydroxy acids), including but not limited to lactic, glycolic and hydroxybutyric acids, polycaprolactones, and polyvalerolactones, can be synthesized or commercially obtained. For example, polyoxyalkylene copolymers are described by U.S. Patent Nos. 3,829,506; 3,535,307; 3,036,118; 2,979,578; 2,677,700; and 2,675,619, the teachings of which are incorporated herein. Polyoxyalkylene copolymers are sold by BASF and others under the tradename PluronicTM. Preferred materials include F-127, F-108, and for mixtures with other gel materials, F-67. These materials are applied as viscous solutions at room temperature or lower which solidify at the higher body temperature. Another example is a low Tm and low Tg grade of styrene-butadiene-styrene block copolymer from Polymer Concept Technologies, C-flexTM. Polymer solutions that are liquid at an elevated temperature but solid at body temperature can also be utilized. For example, thermosetting biodegradable polymers for in vivo use are described in U.S. Patent No. 4,938,763 to Dunn, et al.

Several divalent ions including calcium, barium, magnesium, copper, and iron are normal constitutents of the body tissues and blood. These ions can be used to ionically crosslink polymers such as the naturally occurring polymers

collagen, fibrin, elastin, agarose, agar, polysaccharides such as hyaluronic acid, hyalobiuronic acid, heparin, cellulose, alginate, curdlan, chitin, and chitosan, and derivatives thereof cellulose acetate, carboxymethyl cellulose, hydroxymethyl cellulose, cellulose sulfate sodium salt, and ethylcellulose. Materials that can be crosslinked photochemically, with ultrasound or with radiation.

Materials that can be crosslinked using light, ultrasound or radiation will generally be those materials which contain a double bond or triple bond, preferably with an electron withdrawing substituent attached to the double or triple bond. Examples of suitable materials include the monomers which are polymerized into poly(acrylic acids) (i.e., Carbopols.TM.), poly(acrylates), polyacrylamides, polyvinyl alcohols, acrylated polyethylene glycols, and ethylene vinyl acetates. Photopolymerization requires the presence of a photosensitizer, photoinitiator or both, any substance that either increases the rate of photoinitiated polymerization or shifts the wavelength at which polymerization occurs. The radiolysis of olefinic monomers results in the formation of cations, anions, and free radicals, all of which initiate chain polymerization, grafting and crosslinking and can be used to polymerize the same monomers as with photopolymerization. Photopolymerization can also be triggered by applying appropriate wavelength to a cyclo-dimerizable systems such as Coumarin and Cinnamic acid derivatives. Alpha-hydroxy acids backbone can be activated to carbonium ion. COOH or SO_3H functionality can be inserted that can be subsequently reacted to amine containing ligands Materials that can be crosslinked by addition of covalent crosslinking agents such as glutaraldehyde.

Any amino containing polymer can be covalently crosslinked using a dialdehyde such as glutaraldehyde, or succindialdehyde. Examples of useful amino containing polymers include polypeptides and proteins such as albumin, and polyethyleneimine. Peptides having specialized function, as described below, can also be covalently bound to these materials, for example, using crosslinking agents, during polymerization.

Polymers with free carboxylic acid or other anionic groups (e.g., sulfonic acid), such as the acrylic acid polymers noted above, can be used alone or added to other polymeric formulations to enhance tissue adhesiveness. Alternatively, materials that have tissue binding properties can be added to or bound to the polymeric material. Peptides with tissue adhesion properties are discussed below. Lectins that can be covalently attached to a polymeric material to render it target specific to the mucin and mucosal cell layer could be used. Useful lectin ligands include lectins isolated from: *Abrus precatroius, Agaricus bisporus, Anguilla anguilla, Arachis hypogaea, Pandeiraea simplicifolia, Bauhinia purpurea, Caragan arobrescens, Cicer arietinum, Codium fragile, Datura stramonium, Dolichos biflorus, Erythrina corallodendron, Erythrina cristagalli, Euonymus europaeus, Glycine max, Helix aspersa, Helix pomatia, Lathyrus odoratus, Lens culinaris, Limulus polyphemus, Lysopersicon esculentum, Maclura pomifera, Momordica charantia, Mycoplasma gallisepticum, Naja mocambique*, as well as the lectins *Concanavalin A, Succinyl-Concanavalin A, Triticum vulgaris, Ulex europaeus* I, II and III, *Sambucus nigra, Maackia amurensis, Limax fluvus, Homarus americanus, Cancer antennarius*, and *Lotus tetragonolobus*.

The attachment of any positively charged ligand, such as polyethyleneimine, polylysine or chitosan to any microsphere or polymeric chain may improve bioadhesion due to the electrostatic attraction of the cationic groups to the net negative charge of the mucus. A surfactant-like molecule bearing positive charge and a hydrophobic core would be compatible with the bilayer membrane. This molecule will distribute its core and the positive charge to minimize energy of interaction and hence will be more tissue adhesive. The mucopolysaccharides and mucoproteins of the mucin layer, especially the sialic acid residues, are responsible for the negatively charged surface layer. Any ligand with a high binding affinity for mucin could also be covalently linked to the polymeric material.

Polymeric materials can also be used as tissue adhesives. In one form, fibrin is used. This has the advantage that it can be formed easily *in situ* using the patient's own fibrinogen, blood or serum, by addition of thrombin and calcium chloride. The materials described above can also be used. Other polymeric tissue adhesives that are commercially available include cyanoacrylate glues, GRF (Gelatin-resorcinol-formaldehyde) and polyethyleneglycol-poly(lactic acid and/or glycolic acid)-acrylates, both of which are applied as liquids and then photopolymerized.

The polymeric material can be designed to achieve a controlled permeability, either for control of materials within the cavity or into the tissue or for release of incorporated materials. There are basically three situations that the polymeric material is designed to achieve with respect to materials present in the lumen: wherein there is essentially passage of only nutrients (small molecular weight compounds) and gases from the lumen through the polymeric material to the tissue lumen surface; wherein there is passage of nutrients, gases and macromolecules, including large proteins and most peptides; and wherein there is passage of nutrients, gases, macromolecules and cells. The molecular weight ranges of these materials are known and can therefore be used to calculate the desired porosity. For example, a macromolecule can be defined as having a molecular weight of greater than 1000 daltons; cells generally range from 600-700 nm to 10 microns, with aggregates of 30-40 microns in size. For passage of cell, the material must possess or develop a macroporous structure.

Formation of Materials which have decreased volume following polymerization

Under certain circumstances it may be useful to produce a polymer *in situ* which occupies a smaller volume than the solution from which it is applied, for example, as an adhesive for the cavity to hold the walls together. The polymerization can be accompanied by "syneresis" or expulsion of water from the polymer, during polymerization. Besides reducing mass of the product, this process may yield porous products that may be desirable for healing. Syneresis occurs when a polymerization reaction occurs with reaction of a large number of

fractional groups per unit volume (high crosslinking density or when dilute solutions of reactants are polymerized and the amount of water in the formulation exceeds the intrinsic swelling capacity of the resulting polymer. The latter may occur, for example, when dilute solutions of PEG-diacrylate are polymerized (e.g., less than or equal to 5% macromer).

VII. Incorporation of Bioactive Agents

A wide variety of bioactive agents can be incorporated into the polymeric material. These can be physically incorporated or chemically incorporated into the polymeric material. Release of the physically incorporated material is achieved by diffusion and/or degradation of the polymeric material; release of the chemically incorporated material is achieved by degradation of the polymer or of a chemical link coupling the bioactive material to the polymer, for example, a peptide which is cleaved *in vivo* by an enzyme such as trypsin, thrombin or collagenase. In some cases, it may be desirable for the bioactive agent to remain associated with the polymeric material permanently or for an extended period, until after the polymeric material has degraded and removed from the site.

In the broadest sense, the bioactive materials can include proteins (as defined herein, including peptides generally construed to consist of less than 100 amino acids unless otherwise specified), saccharides, polysaccharides and carbohydrates, nucleic acids, and synthetic organic and inorganic materials, or combinations thereof.

Specific materials include antibiotics, antivirals, antiinflammatories, both steroidal and non-steroidal, antineoplastics, anti-spasmodics including channel blockers, modulators of cell-extracellular matrix interactions including cell growth inhibitors and anti-adhesion molecules, enzymes and enzyme inhibitors, anticoagulants, growth factors, DNA, RNA antisense, ribozymes, aptamers, and protein synthesis inhibitors, anti-cell migratory agents, anti-proliferative agents, vasodilating agents, and other drugs commonly used for the treatment of injury to tissue. Examples of these compounds include angiotensin converting enzyme

inhibitors, anti-thrombotic agents, prostacyclin, heparin, salicylates, thrombolytic agents, anti-proliferative agents, nitrates, calcium channel blocking drugs, streptokinase, urokinase, tissue plasminogen activator (TPA) and anisoylated plasminogen activator (TPA) and anisoylated plasminogen-streptokinase activator complex (APSAC), GPIIb/IIIA antagonists, colchicine and alkylating agents, growth modulating factors such as interleukins, transformation growth factor .beta. and congeners of platelet derived growth factor, fibroblast growth factor, epidermal growth factor, hepatocyte scatter factor, leptin, monoclonal antibodies directed against growth factors, modified extracellular matrix components or their receptors, lipid and cholesterol sequestrants, matrix metalloproteases (MMPs), collagenase, plasmin and other agents which may modulate tissue tone, function, and the healing response to organ injury post intervention. Additional examples of such compounds include nitric oxide containing, releasing or producing materials, antiproliferatives as well as antioxidants, a number of which are known.

Hormones, especially reproductive or sex homones, may be particularly advantageous to deliver using these materials. It may also be useful to deliver chemotherapeutics such as BCNU, cisplatin, taxol, Actinomycin D, and other cytotoxic agents. Also addition of stress response inducing agents, evoking heat shock or other mammalian stress protein responses may be desired. Agents include organic and inorganic manganese, tin, cadmium compounds, geldanamycin and analogues oxidizing agents e.g. hydrogen peroxide. Further stress response proteins may also be administered. In certain situations inhibitors of these inducers and of the stress response may also be delivered.

Materials such as attachment peptides (such as the FN cell-binding tetrapeptide Arg-Gly-Asp-Ser (RGDS)), selectin receptors and carbohydrate molecules such as Sialyl Le.sup.x, can be used which serve to attract and bind specific cell types, such as white cells and platelets. Materials such as fibronectin, vimentin, and collagen, can be used to non-specifically bind cell types, to enhance healing. Other proteins known to carry functional RGD

sequences include the platelet adhesion proteins fibrinogen, vitronectin and von Willebrand factor, osteopontin, and laminin. Specific RGD peptides are described in U.S. Patent Nos. 4,517,686 to Ruoslahti, et al., 4,589,881 to Pierschbacher, et al., 5,169,930 to Ruoslahti, et al., 5,149,780 to Plow, et al., 4,578,079 to Ruoslahti, et al., 5,041,380 to Ruoslahti, et al., and Pierschbacher and Ruoslahti, J. Biol. Chem. 262(36), 17294-17298 (1987), Mohri, et al., Amer. J. Hem. 37:14-19 (1991), Aumailley, et al., FEBS 291(1), 50-54 (1991), Gurrath, et al., Eur. J. Biochem. 210, 911-921 (1992), and Scarborough, et al., J. Biol. Chem. 268(2), 1066-1073 (1993). Laminin promotes cell adhesion, migration, differentiation, and growth (Kleinman, et al., J. Cell Biochem. 27:317-325 (1985); Kleinman, et al., Biochem. 25:312-318 (1986); Beck, et al., FASEB J. 4:148-160 (1990). The nonapeptide CDPYIGSR promotes cell attachment and migration (Graf, et al., Cell 48:989-996 (1987), Biochem. 26:6896-6900 (1987)). Further studies have shown that YIGSR-containing peptides can inhibit angiogenesis and tumor metastasis (Grant, et al., Cell 58:933-943 (1989), Iwamoto, et al., Science 238:1132-1134 (1987), Sakamoto, et al., Cancer Res. 51:903-906 (1991). Other peptides include PDSGR and IKVAV. Integrins typically bind to cell adhesion proteins via the rather highly conserved sequence Arg-Gly-Asp X (RGDX), where X is variant depending on the particular cell adhesion protein.

Cells to be incorporated include stromal cells and/or fibroblasts or other mesenchymal cells to facilitate closure of tissue voids. Alternatively glandular epithelial cells, either mature, developing, embryonic/fetal or genetically engineered, may be deposited. These may serve to alter regional or systemic physiology through endocrine or paracrine hormone or other mediator release. Further, neural cells, precursors or tissues may be implanted to facilitate reinnervation and or local adrenergic, cholinergic or other neurotransmitter responses.

In a preferred embodiment, a combination of factors and cells are used to induce angiogenesis in the endomural zone or access tract to the zone.

Exemplary angiogenic growth factors include FGF, PDGF, EGF, VEGF, Midkine chemokines, leptins , angiopoeitin, and other growth factors, inflammatory angiogenic polymers or polymer constructs, electoactive or other microinjurious or locally stimulatory polymers. Preferred cells include endothelial cells, EC bone marrow precursor cells, other stems cells smooth muscle cells or precursors, combinations, neural cells or neural stem cells or combinations with above are placed. These are used for example for angiogenesis, myogenesis or myocardial tissue repair in which myocytes – precursor, differentiated, homograft, isograft, allograft or xenograft are placed in the myocardium, with or without polymer adducts or matix protein mixtures, or with neural cells or other adrenerically active or cholinergically active cell types. Means (hard wire or polymer) for electrically driving, pacing, shocking or sensing the neotissue can also be included.

Essentially the same techniques can be used for nerve regeneration or tissue reinnervation by implanting neurons, Schwann cells, astrocytes, glial cells and/or angiogenic precursors. In one embodiment, the nerve cells are administered with polymer matrices, which may include or be formed of bioactive, biodegradable biostable polymers such as polyethyleneglycol polymers, hyaluronic acid, and laminins.

In yet another embodiment, these techniques are used for local endomural delivery of stress response inducing agents or actual stress response proteins. Both physical and chemical stimuli can be used to induce expression of heat shock proteins. The most frequently studied stimuli are heat, oxidants, and heavy metals. Alternatively, or in addition, heat shock proteins can be directly administered to the cells to be treated. Those that are believed to correlate with a response to injury include hsp70, hsp 90 and other cytoplasmic heat shock proteins. Assays to measure the levels of these proteins are well known to those skilled in the art. However, it should be noted that the inducement of heat shock proteins may not be the actual mechanism by which a

beneficial effect is obtained, but merely an indicator that appropriate conditions have been used which result in the desired beneficial effect.

Several reviews of heat shock proteins have been published, including Schlesinger, Heat Shock: from bacterial to man (Cold Spring Harbor, Cold Spring Harbor, NY 1982); Lindquist, Ann. Rev. Biochem. 55:1151-1191 (1986); Pelham, H.R.B., Cell 46, 959-61 (1986); Lindquist and Craig, "The heat-shock proteins" Annu. Rev. Genet. 22:631-677 (1988); Pelham, EMBO J. 8:3171-3176 (1989); Schlesinger J. Biol. Chem. 265:12111-12114 (1990); Kaufmann, Immunol. Today 11:129-137 (1990); Morimoto Cancer Cells 3:295-301 (1991); Nover, "HSFs and HSPs - a stressful program on transcription factors and chaperones." Stress Proteins, and the Heat Shock Response, sponsored by Cold Spring Harbor Laboratory (Cold Spring Harbor, NY USA April 29-May 2, 1991) Nature New Biol. 3:855-859 (1991); and Nover and Scherf "Heat shock protein, in Heat Shock Response (CRC Press, 1991) pp. 41-127.

In most cases, it is possible to physically incorporate the bioactive agent by mixing it with the material prior to application to the tissue surface or within the cavity and polymerization or solidification. The material can be mixed into the monomer solution to form a solution, suspension or dispersion. In another embodiment, the bioactive agent can be encapsulated within delivery devices such as microspheres, microcapsules, liposomes, cell ghosts or psuedovirions, which in themselves affect release rates and uptake by cells such as phagocytic cells.

Bioactive agents can be chemically coupled (conjugated) to the polymeric material, before or at the time of polymerization. Bioactive materials can also be applied to the surface of catheters, trocars, endoscopes, stents or tissue seals or plugs or sensing implants used in the procedures described herein, alone or in combination with the polymeric materials. Cathcter and other device or implant bodies are made of standard materials, including metals such as surgical steel and thermoplastic polymers. Occluding balloons may be made from compliant materials such as latex or silicone, or non-compliant materials

such as polyethylene terephthalate (PET). The expansible member is preferably made from non-compliant materials such as PET, (PVC), polyethylene or nylon. The balloon catheter portion may optionally be coated with materials such as silicones, polytetrafluoroethylene (PTFE), hydrophilic materials like hydrated hydrogels and other lubricous materials to aid in separation of the polymer coating. Seals and plugs may be made of structural biodegradable or biostable polymers as listed above or from hydrogels polymerized in situ, polymerized ex vivo and transported locally or dessicated hydrogels or organogels or mixtures of the above. Sensing/telemetring implants may be made of combinations of polymeric and microeletronic, microchip, MEMS or other semiconductor type components.

Several polymeric biocompatible materials are amenable to surface modification in which surface bound bioactive molecules/ligands exhibit cellular binding properties. These methods are described by Tay, Merrill, Salzman and Lindon in Biomaterials 10, 11-15 (1989). Covalent linkages can be formed by reacting the anhydride or acid halide form of an N-protected amino acid, poly(amino acid) (two to ten amino acids), peptide (greater than 10 to 100 amino acids), or protein with a hydroxyl, thiol, or amine group on a polymer. The amine groups on the amino acid or peptide must be protected before forming the acid halide or anhydride, to prevent self-condensation. N-protection is well known by those skilled in the art, and can be accomplished by use of various protecting groups, such as a carbobenzoxy (CBZ) group. The term "protecting group" as used herein refers to a moeity which blocks a functional group from reaction, and which is cleavable when there is no longer a need to protect the functional group. Examples of functional groups include, but are not limited to, amino, hydroxy, thio, and carboxylate groups. Examples of protecting groups are well known to those skilled in the art. A carboxyl-containing compound can contain various functional groups, such as hydroxy, thio, and amino groups, that can react with an acid halide or anhydride. These functional groups must be protected before forming an acid chloride or anhydride to avoid self-

condensation. After formation of the acid chloride or anhydride, and subsequent reaction with the hydroxyl, thiol, or amino group(s) on another molecule, the protecting group can be removed in a "deprotecting" step. The N-protected amino groups can be deprotected by means known to those skilled in the art. Any hydroxy or thio groups on these compounds must be protected so as not to react with the acid halides or anhydrides. Examples of suitable protecting groups for alcohols include but are not limited to trialkyl silyl groups, benzyl ethers, and tetrahydropyranyl ethers. These groups can be protected by means known to those skilled in the art, and can be subsequently deprotected after the esterification is complete. Examples of protecting groups can be found in Greene, T. W., and Wuts., P; G. M., "Protective Groups in Organic Synthesis 2d Ed., John Wiley & Sons, Inc., pp. 317-318 (1991), hereby incorporated by reference. A method for preparation of acid halide derivatives is to react the carboxylic acid with thionyl chloride, preferably in benzene or toluene with a catalytic amount of DMF. A known method for producing anhydrides is to react the carboxylic acid with acetic anhydride. In this reaction, as acetic acid is formed, it is distilled out of the reaction vessel. Peptides can be covalently bound to the polymeric material, for example, when the polymeric material is a polymer of an alpha hydroxy acid such as poly(lactic acid), by protecting the amine functionality on the peptide, forming an acid halide or anhydride of the acid portion of the polymer, reacting the acid halide or anhydride with free hydoxy, thiol, or amine groups on the polymer, then deprotecting the amine groups on the peptide to yield polymer having peptide bound thereto via esterification, thioesterification, or amidation. The peptide can also be bound to the polymer via a free amine using reductive amination with a dialdehyde such as glutaraldehyde. The ester groups on a polyester surface can be hydrolyzed to give active hydroxy and carboxyl groups. These groups can be used to couple bioactive molecules. Preferably, before converting the active carboxylate group to the acid halide or anhydride form, the active hydroxy group is protected to avoid reaction with the resulting acid halide or anhydride. As a non-limiting

example, the active hydroxy group can be protected as a benzyl ether. The active carboxyl group can then be converted to the acid halide or anhydride, and reacted with a hydroxy or amino group on a second compound to form an ester or amide linkage. The O-protected hydroxy group can then be deprotected.

Coupling agents such as carbodiimides, diisocyanates, or organosilanes can be used to bind polymers, or metals and ceramics to bioactive agents covalently. For example, a metal stent may be treated with an aqueous solution of an aminotrialkoxy silane. These form an amino functional surface which can react with carboxy-functional proteins, for durable attachment or controlled release. Carbodiimides can react with carboxyl functional groups to produce amino-reactive intermediates. Carboxy functional polymers can be reacted to form N-hydroxy succinimide esters which are very reactive with amino groups on peptides. This chemistry has been used to form surgical sealants PEG-di-N-hydroxysuccinimide and albumin, Barrows, et al., 3M Corporation, but could be used to couple bioactive molecules to polymers.

2. Application of Polymeric Materials

In general terms, the polymeric material is a biocompatible polymeric material having a variable degree of fluency in response to a stimulus or mechanical pressure, as described above. The material is such that it is substantially non-fluent *in vivo* upon completion of the coating process. The material, in its fluent form or a conformable form, is positioned in contact with a tissue or device surface to be coated and then stimulated to render it non-fluent or conformed, as described above. The polymeric material is applied to the cavity or endomural void using catheters, syringes, or sprays, depending on the tissue surface or device to which it is applied, using the devices described above or devices known to those skilled in the art.

The coating typically will be applied to a tissue surface such as the media of an artery, the urethra, brain or the myocardium using some type of catheter, trocar or scope. The coating material is preferably applied using a single catheter or similar device with single or multiple lumens. The catheter

should be of relatively low cross-sectional area. A long thin tubular catheter manipulated using endoscopic guidance is preferred for providing access to the interior of organ areas. Alternatively the device may have direct vision capabilities via contained fiberoptics or actual tip cameras (CCD, C-MOS,etc) or via echo sensing, US sensing or GPS positioning systems.

Application of the coating material may be accomplished by extruding a solution, dispersion, or suspension of monomers, polymers, macromers, or combinations thereof through a catheter to coat or fill a tissue surface or cavity, then controlling formation of the coating by introducing crosslinking agents, gelling agents or crosslinking catalysts together with the fluent material and then altering the conditions such that crosslinking and/or gelling occurs. Thus, when a balloon catheter is used, a flow of heated or chilled fluid into the balloon can alter the local temperature to a level at which gelling or cross-linking is induced, thereby rendering the material non-fluent. Localized heating or cooling can be enhanced by providing a flow of heated or chilled liquid directly onto the treatment site. Thermal control can also be provided, however, using a fluid flow through or into the balloon, or using a partially perforated balloon such that temperature control fluid passes through the balloon into the lumen. Thermal control can also be provided using electrical resistance heating via a wire running along the length of the catheter body in contact with resistive heating elements. This type of heating element can make use of DC or radio frequency (RF) current or external RF or microwave radiation. Other methods of achieving temperature control can also be used, including light-induced heating using an internal optical fiber (naked or lensed). Altrnatively as self-contained fluid flow system allowing inflow and outflow of fluids to the ballon, actuator or other material applying tip of surface may control polymer flow, melt, setup and cooling and fixation. The polymer formulation can contain components which convert light into heat energy. Similar devices can be used for application of light, ultrasound, or irradiation.

Alternatively the polymers may be delivered as solid materials of various configurations e.g. rods, speheres, folded sheets, yarms, meshes, twines, ropes, particles , amorphous shapes, flakes, etc. Similarly hydrogel materials may be dlivered with the above physical geometries in either the hydrated, partially hydraed or dessicated form. Further defined hydrogel shapes shuch as spikes, spheres with wicks and other tract + void shapes may be delivered for the purpose of void sealing or plugging or repair.

Any of the foregoing materials can be mixed with other materials to improve their physiological compatibility. These materials include buffers, physiological salts, conventional thickeners or viscosity modifying agents, fillers such as silica and cellulosics, and other known additives of similar function, depending on the specific tissue to which the material is to be applied.

The process of fixing the shape of the polymeric material can be accomplished in several ways, depending on the character of the original polymeric material. For example, a partially polymerized material can be expanded using a balloon after which the conditions are adjusted such that polymerization can be completed, e.g., by increasing the local temperature or providing UV or visible radiation through an optical fiber. A temperature increase might also be used to soften a fully polymerized sleeve to allow expansion and facile reconfiguration and local molding, after which it would "freeze" in the expanded position when the head source is removed. Of course, if the polymeric sleeve is a plastic material which will permanently deform upon stretching (e.g., polyethylene, polyethylene terephthalate, nylon or polyvinyl chloride), no special fixation procedure is required.

The present invention will be further understood by reference to the following non-limiting examples.

Example 1: Application of tissue adhesive in a cavity.

An incision in an organ is made. A tissue adhesive is then applied within the cavity to enhance healing of the wound. The following are examples of useful tissue adhesives to close the voids.

a. 1 gm of 50 mg Fibrinogen/ml is mixed in situ with 0.3 g of 150 NIH U thrombin/ml containing 100 mM $CaCl_2$ at the site of the cavity. This forms a tissue glue within 90 sec.

b. 2 gm of 100 mg Fibrinogen/ml is mixed in situ with 0.3 g of 150 NIH U thrombin/ml containing 100 mM $CaCl_2$ at the site of the cavity. This forms a tissue glue within 30 sec.

c. 1 gm of 50 mg Fibrinogen/ml is supplemented with 2500 kIU Aprotinin/ml with 12.5 mg epsilon-aminocaproic acid/ml. The solution is mixed *in situ* with 0.3 g of 150 NIH U thrombin/ml containing 100 mM $CaCl_2$ at the site of the cavity. This will delay the *in vivo* degradation of Fibrin glue and retain the collapsed state of the cavity for a longer duration of time. Tranexamic acid can be used instead of aprotinin for better healing response of the tissue.

Example 2: Dehydration of tissue before application of glue.

In another example, a cavity is aspirated following washing with a concentrated ethanol solution (80% w/w in water). This process dehydrates the local area of the cavity. The in situ Fibrin glue is applied as described above to promote better adhesion of the tissue.

Modifications and variations of the methods and compositions described above will be obvious to those skilled in the art and are intended to be encompassed by the following claims.

We claim:

1. A method of treatment comprising locally penetrating and entering the body of an organ, organ component or tissue structure with minimal damage to obtain access to endomural zones of an organ.

2. The method of claim 1 further comprising depositing in the midzone therapeutic agents and systems.

3. The method of claim 2 wherein the therapeutic agents are selected from the group consisting of drugs, cells and polymers and diagnostic and/or therapeutic devices.

4. The method of claim 3 wherein the polymers may be degradable or non degradable.

5. The method of claim 3 wherein the polymers are selected from the group consisting of solid matrices, porous matrices, hydrogels, organogels, colloidal syspensions, microparticles and microcapsules, anoparticles and combinations therof.

6. The method of claim 3 wherein the drugs are selected from the group consisting of anti-infectives, antibiotics, antifungal, antihelminthic, antiparasistic agents, anticancer agents, anti-proliferative agents, anti-migratory agents, anti-inflammatory agents, metalloproteases, proteases, thromblytic agents, fibrinolytic agents, steroids, hormones, vitamins, charbohydrates, lipids proteins, peptides and enzymes.

7. The method of claim 3 wherein the drugs are proliferative growth factors selected from the group consisting of PDGF, FGF, TGF, EDGF, Epidermal GF, NGF, ILGF, Hepatocyte scatter factor, angiogenic growth factors, serum factors, collagen, laminin, tenascin, SPARC, thrombospondin, fibronectin, vimentin and other matrix factors.

8. The method of claim 3 wherein the cells are selected from the group consisting of autogenous similar cells (i.e. mesenchymal for mesenchymal) from adjacent normal zones of the same or different organs.

9. The method of claim 3 wherein the cells are selected from the group consisting of autogenous differing cells (i.e. mesenchymal for ectodermal or splenocytes for endothelial cells) from adjacent normal zones of the same or different organs.

10. The method of claim 3 wherein the cells are therapeutic factors produced by or in the form of stem cells or other progeneitor cells.

11. The method of claim 3 wherein the cells are explanted and clonally or otherwise expanded *in vitro* for implantation, either without genetic modification or genetically modified, before implantation.

12. The method of claim 3 wherein the therapeutic factors are selected from the group consisting of genes, plasmids, episomes, viruses, viroids, or other microorganisms for therapeutic or synthetic purpose.

13. The method of claim 3 wherein the therapeutic factors are heat shock or stress response proteins or inducers of heat shock or stress response proteins.

14. The method of claim 1 further comprising where a cavity or containment space or reservoir area does not exist in the endomural zone, creating such a space for therapeutic placement.

15. A device comprising a hollow tubular member with an end penetrating or cuting means causing minimal collateral damage and means for delivery of therapeutic agents into endomural tissue.

16. The device of claim 15 wherein the member is rigid made of metal, polymer, or composite.

17. The device of claim 15 wherein the member is flexible and comprises a catheter-like device.

18. The device of claim 15 wherein the member is attached to a single or multiple reservoirs for therapeutic agent containment and delivery.

19. The device of claim 15 wherein the member has an expansile cutter at the distal end to create a tissue space.

20. The device of claim 15 further comprising diagnostic or therapeutic sensors.

21. The device of claim 15 further comprising projectile means to ballistically transfer particles through the ectoluminal or endoluminal zone for retention in the endomural zone.

22. The device of claim 21 wherein the projectile means is selected from the group comprising mechanical acceleration, electrical transfer, spark explosion, and gas explosion.

23. The device of claim 15 further comprising means for indirect or direct guidance means.

24. The device of claim 23 wherein the means for direct guidance is selected from the group consisting of fiber optic imaging systems, endoscopes, direct tip cameras, CCD, C-MOS or other chip or electrical video systems, ultrasound or GPS positioning systems.

25. The device of claim 15 in a kit comprising a void filling material which contains electroactive agents.

26. The device of claim 15 comprising a void filling material or implant which can locally sense, store or telemeter physical, chemical or biological information.

27. The device of claim 15 comprising electoactive or electroconductive polymers which may be directly or externally activated via transcutaneous energy delivery to elicit positive or negative galvanotaxis (tissue healing or cell movement to or from based on local persistent or intermittent electrical current).

28. The device of claim 15 comprising a therapeutic for induction of angiogenesis or myogenesis.

29. The device of claim 28 comprising a therapeutic selected from the group of angiogenic growth factors, inflammatory angiogenic polymers or polymer constructs, electoactive or other microinjurious or locally stimulatory polymers.

30. The device of claim 28 comprising cells selected from the group consisting of endothelial cells, EC bone marrow precursor cells, other stems cells smooth muscle cells or precursors, combinations, neural cells or neural stem cells or combinations with above are placed.

31. The device of claim 15 for nerve regeneration.

32. The device of claim 15 comprising a bioactive polymer.

33. The device of claim 15 comprising stress response inducing agents or actual stress response proteins.

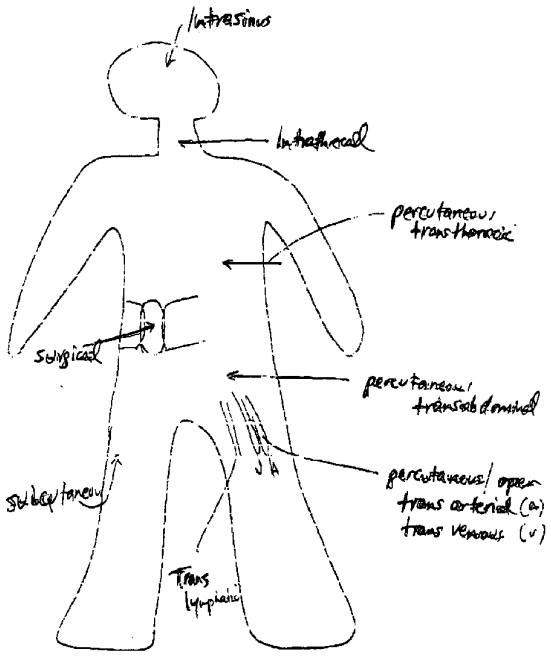
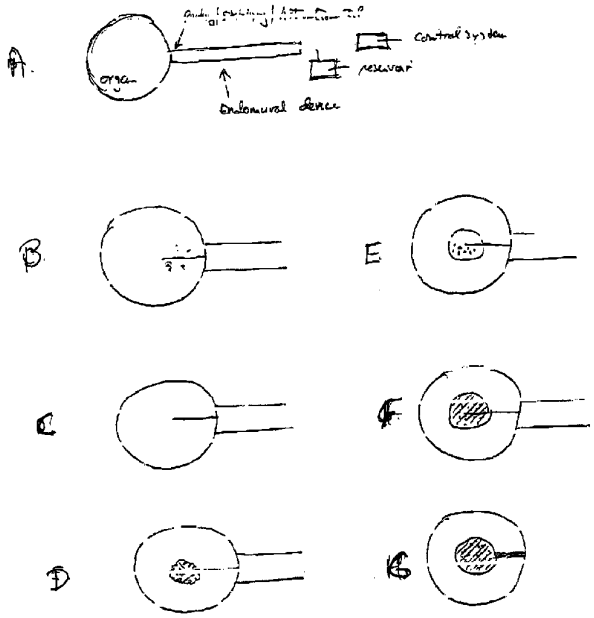

Intravenous
Intrathecal
percutaneous/ transthoracic
surgical
percutaneous/ transabdominal
percutaneous/ open trans arterial (a) trans venous (v)
subcutaneous
Trans tympanic

FIGURE 1


A
organ
control system
reservoir
endonuminal device
B
E
C
F
D
G

Figures 2A-G

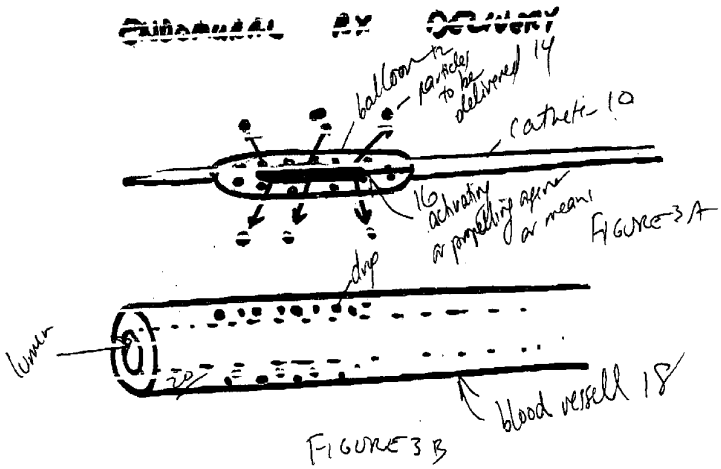


FIGURE 3A

FIGURE 3B

ELECTRO - HYDRAULIC

PNEUMO - HYDRAULIC

(ELECTROPORATION)

Figure 3A & 3B

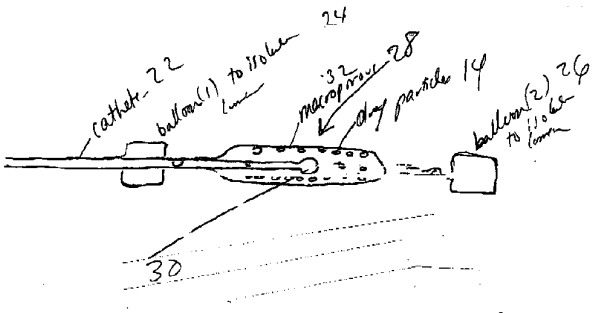


Figure 4A

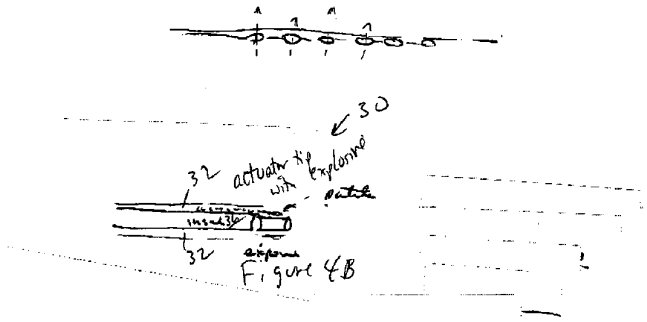


Figure 4B

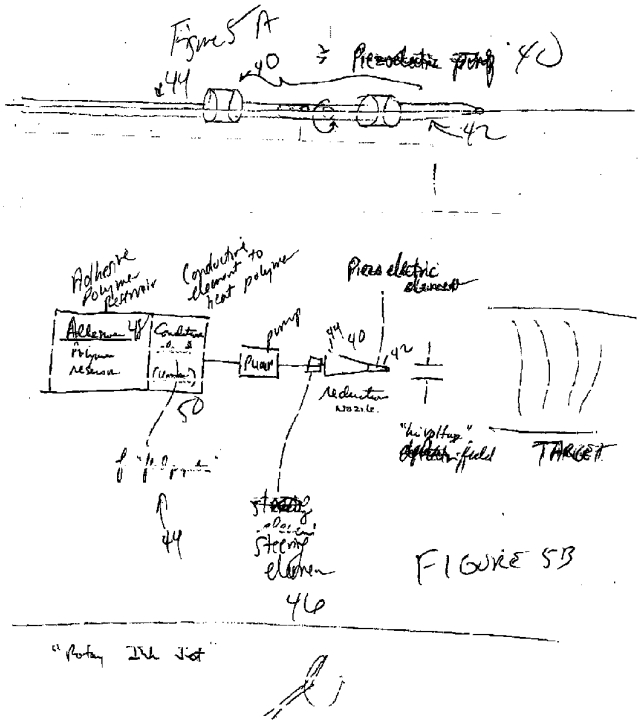


Figure 5A
40
42
44
Piezoelectric pump 40
Adhesive polymer reservoir
Conductive element heat polymer
Piezo electric element
pump
Pump
50
TARGET
Steering element
46
FIGURE 5B

【国際公開パンフレット（コレクトバージョン）】

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 August 2002 (22.08.2002)

PCT

(10) International Publication Number
WO 2002/064014 A2

(51) International Patent Classification⁷: A61B

(21) International Application Number:
PCT/US2002/003726

(22) International Filing Date: 8 February 2002 (08.02.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/267,578 9 February 2001 (09.02.2001) US

(71) Applicant: ENDOLUMINAL THERAPEUTICS, INC. [US/US]; 5001 North Summit Ridge Road, Tucson, AZ 85750 (US).

(72) Inventor: SLEPIAN, Marvin, J.; 5001 North Summit Ridge Road, Tucson, AZ 85750 (US).

(74) Agents: PABST, Patrea, L. et al.; Holland & Knight LLP, One Atlantic Center, Suite 2000, 1201 West Peachtree Street, N.E., Atlanta, GA 30309-3400 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

(48) Date of publication of this corrected version:
29 January 2004

(15) Information about Correction:
see PCT Gazette No. 05/2004 of 29 January 2004, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2002/064014 A2

(54) Title: ENDOMURAL THERAPY

(57) Abstract: Methods, devices and materials for the treatment or repair, replacement, transplantation or augmentation of tissues in endomural zones specifically by open surgical, minimally invasive or percutaneous transmural or trans parenchymal application of polymeric material alone or in combination with bioactive agents or cells, have been developed. These methods and systems are useful to repair, after function, replace function or augment function of the central or endomural aspects of solid organs or tubular body structures.

ENDOMURAL THERAPY

Background of the Invention

This invention relates to an aspect of *in situ* tissue engineering of organs or organ components, and repair, replacement, or alteration of function via manipulations targeted to the middle or endomural aspects of tissues.

This application claims priority to U.S.S.N. 60/267,578 filed February 9, 2001.

This invention relates to devices, materials and methods for the treatment or repair of tissues, specifically by accessing the endomural zone (middle zone) of organs, organ components or tissues, either via surgical or percutaneous application of devices, polymeric materials, alone or in combination with bioactive agents or cells.

Many diseases involve the central aspects of organs, e.g. tumors in the liver, atherosclerotic lesions within the walls of arteries, adenomas in the prostate, malignancies within the brain, etc. Today the majority of these types of lesions are removed via open surgical, minimally invasive or percutaneous procedures which make direct incisions into the organ beginning on the ectoluminal or endoluminal surface. As such these approaches remove much healthy tissue in surrounding unaffected tissue layers, in the process of removing or treating the diseased zone. For example, in open surgical removal of an intra-organ tumor the capsule and ectoluminal zones as well as surrounding endomural healthy zones are often violated and excised in the process of removing the contained disease zone. While this therapy is effective it has the added morbidity burden of "mass" rather than "selective" destruction or treatment.

The same issue of unnecessary tissue damage and removal holds true for percutaneous or endoluminally accessed and treated disease. Access to the endoluminal regions via this route has traditionally removed the overlying endoluminal layers and surrounding endomural healthy zones to get at diseased zones within. An example of this may be seen in the current therapy for

prostatic adenomas, the TURP (Transuretheral resection of the Prostate) procedure. In TURP the normal urothelial mucosal layer is removed as well as the peri-urethral column to gain access and remove intra-organ contained adenomas. This approach, while effective in removing the contained disease zone, unfortunately removes a significant amount of normal non-diseased tissue at the same time. As such, current procedures carry unnecessary morbidity and mortality due to their invasiveness and associated trauma.

Another limitation of current therapies lies in the fact that many diseases involve cellular derangement in the endomural zones while current therapies often only treat outer, either endoluminal or ectoluminal, zones. An example of this may be seen in therapy of atherosclertic lesions of coronary and peripheral arteries. In cases of severe atherosclerotic obstruction, endovascular removal of obstructive lesions via endovascular atherectomy, a catheter-based shaving, coring or drilling procedure from within the vessel is often employed. These approaches remove the diseased atheroma close to the vessel lumen and close to the treatment device. However, they do not tackle the source or "core' of the disease which frequently lies in the media of the artery, the endomural zone of the vessel.

Many therapies today are administered systemically with the goal of achieving a local intra-organ effect. If systems and methods existed which would provide mechanical physical targeting with simultaneous sustained intra-organ presence more effective, more accurate, site specific therapies would be achieved. Many "local" therapies are not local but regional and in fact affect adjacent zones. An example of this is intra-arterial chemotherapy for intra-hepatic malignancy such as hepatoma or hepatic metastasis. In this therapy drugs are adminstered via the hepatic arterial or vasculature system to treat disease within the organ but in fact the entire organ from within and without is bathed with medication. Further hepatically delivered medication subsequently diffuses or mixes directly intralumenally with systemic blood.

It is therefore an object of the present invention to provide methods and devices for treatment of diseased organs or tissues with minimal damage to surrounding tissue.

It is a further object of the present invention to provide methods and devices for treatment of cental, core or generally "endomural" zones of diseased organs or tissues with minimal damage to surrounding tissue

It is a further object of the present invention to provide methods and devices for treatment of specific tissues while avoiding systemic toxicity.

It is a further object of the present invention to provide polymeric materials, drugs and biologically active compositions which can be delivered or released endomurally to aid in healing.

It is a still further object of the present invention to provide devices, both surgical and percutaneous to access and modify endomural tissues and/or deliver polymeric materials, drugs and biologically active compositions which can be delivered or released endomurally to aid in healing.

Summary of the Invention

Methods, devices and materials for the treatment or repair, replacement, transplantation or augmentation of tissues in endomural zones specifically by open surgical, minimally invasive or percutaneous transmural or trans parenchymal application of polymeric material alone or in combination with bioactive agents or cells, have been developed. These methods and systems are useful to repair, alter function, replace function or augment function of the central or endomural aspects of solid organs or tubular body structures.

Brief Description of the Drawings

Figure 1 is a diagram of a patient showing the various means of accessing the endomural zones: intra sinus, intrathecal, percutaneous transthoracic, percutaneous transabdominal, percutaneous - open, transarterial, transvenous, translymphatic, subcutaneous, and surgical.

Figures 2A-G are diagrams showing introduction of bioactive material using a catheter including a reservoir and control means to access the organ (A),

where the catheter is positioned and stabilized (B), the endoluminal zone penetrated (C), stabilized in the endomural zone (D), optionally further including the step of removing tissue, using mechanical, laser, thermal, radiofrequency, ultraviolet, x-ray, electromagnetic, acoustic or chemical means (E), delivering biologically active agents, including pharamcologic agents, cells, or biomaterials (G), and sealing the zone and access tract (H).

Figures 3A and 3B a catheter including expansive means for delivery of drug particles (Figure 3A) into the endomural zone (Figure 3B).

Figures 4A and 4B are a catheter including an actuator means for expanding expansive means for delivery of drug particles into the endomural zone (Figure 4A) and an expanded view of the actuator means (Figure 4B).

Figures 5A and 5B are a catheter including a piezoelectric pump (Figure 5a), where the catheter further includes a spray nozzle for dispensing drug particles into endomural tissue, guide means, and a reservoir for fluids or polymer and an optional heating element for melting of the polymer.

Detailed Description of the Invention

A method has been developed for treatment of endomural tissue. The method generally include placing a tubular tissue accessing device (needle, trocar, catheter) percutaneously into the organ. Tissue is removed in the organ. A flowable preformed or dessicated hydrogel or solid polymer plug is placed into the hole, filling the void and sealing the tissue tract. This method is useful in a variety of applications. For example, the endocardial (or epicardial) surface is accessesed via delivery device, the device is stabilized against the heart wall, the myocardium is penetrated to access the endomural zones, a space or void is created, and cells, polymers,drugs and genes or combination of these in varying sequences can delivered to the myocardium. The void mass or plug is then sealed in place.

This method is generally shown in Figure 1 and Figures 2A-2G. The method includes the steps of:

1. Access close to organ, either percutaneously, surgically, laparoscopically, transvacularly, transenterally, intrathecally, subcutaneously via tissue planes, translyphatically,etc.

2. Park and stabilize in location the delivery means.

3. For endo or ecto access, penetrate endoluminal zone, stabilize in endomural zone, locally treat tissue, and remove tissue – mechanically, thermally, with laser, radiofrequency, ultraviolet, x-ray (any form of tissue damaging), electromagnetic energy, acoustic energy (ultrasound), dessication, gas exposure (CO_2, ether), chemically – antimetabolics, antineoplastic, anti-inflammatory, antimicrobial, antiviral, antibiotics, hormones, antibodies, etc.

4. Deliver agents, such as pharmacologic agents, cells, or other biologicals or biomaterials.

5. Seal zone and access tract.

Definitions

I. General Organization of Higher Animals:

The structural organization of higher animals such as mammals, including man, is that of multiple integrated and interactive tissue components. These tissues may be organized as discrete organs which are functional factories, e.g. liver producing biochemical mediators or device systems, e.g. heart – mechanically pumping blood and brain – electrically signaling and coordinating events. As referred to herein, organs include solid and hollow organs, e.g. the liver and colon, respectively.

Alternatively, animals contain tissue components which are largely conduits for functional fluids such as blood, lymph, endocrine or exocrine secretions or gases. These tubular "organ components" or conduits are structures such as arteries, veins, lymphatics, bile ducts, ureters, fallopian tubes, etc.

II. Structure of Organs and Organ Components – The Endomural Zone Defined

Discrete organs may be generically described as having three regions or zones. These regions include: 1. the ectoluminal or outer zone (i.e. capsule, serosa, etc.), 2. the endomural or middle zone and 3. the endoluminal zone. In discrete organs the ectoluminal region typically functions to protect and contain the organ. The endomural zone of the organ is typically the functional or "business end," of the organ, acting as a biochemical factory for production of homeostatic proteins, hormones, enzymes and immunoglobulins for defense and reparative cells for tissue repair, organ regeneration, , metabolism or other specialized functions. In mechano-dynamic organs such as the heart and lung, the endomural zones function to propel or exchange fluid or gas. The inner or ectoluminal zone of organs may have functions similar to the endomural zone or act as yet another internal boundary or barrier layer. If an organ is cut in cross-section the ectoluminal zone may be characterized as the outer 10% ± 10 cross-sectional area, the endomural zone as the mid 80% ± 10 and the endoluminal zone as the inner 10% ± 10.

In addition to solid or hollow organs with cavities true tubular organs and organ components exist as vital body structures. Examples of tubular organs include the small intestine and the colon. Tubular organ components include major interpenetrating blood vessels in organs, e.g. the portal vein in the liver, the cavernous sinus in the brain. Examples of tubular tissue structures, include ducts, e.g. the bile duct, or blood vessels, e.g., arteries or veins.

. Tubular organs and tissue structures in general have a laminated, multi-layer "tube-in-tube' structure made of at least three layers. All of these tubular organs, organ components or tissue structures may be characterized in similar fashion as outlined for organs above into ectoluminal, endomural and endoluminal zones. In tubular structures the ectoluminal zone may be characterized as the outer 10% ± 10 cross-sectional area, the endomural zone as the mid 80% ± 10 and the endoluminal zone as the inner 10% ± 10. Interestingly, tubular organs and tissue structures have defined histologic layers which generally correlate with these zones. The ectoluminal zone correlates

with serosa or adventitia. The endoluminal zone correlates with the lamina propria, submucosa, muscularis, or media. The endoluminal zone correlates with the intima or mucosa.

Methods of Treatment

I. Localized Treatment

Methods which focus on treatment of the endomural region of an organ or tissue provide a means to reduce the trauma to adjacent, contiguous or "collateral," healthy tissue associated with removing, containing or locally treating active disease within central or endomural regions of an organ or tissue structure. This also allows the disease to be treated more effectively, on a local basis, with agents, cells or systems without risk of systemic exposure. Through local application of polymers, pharmaceuticals, genes, therapeutic peptides, cells, radiation systems, etc., one is able to focus therapy to the affected zone of an organ while sparing exposure of surrounding contiguous or adjacent healthy tissue. Local intra-organ therapy reduces systemic exposure to agents which may have deleterious effects systemically. This allows application of higher effective concentration of agents without fear of toxicities with reduced systemic spillover effects.

Endomural treatment also provides a means for sustained durable local therapy, as well as containment and hence sustained exposure or therapeutic presence in an organ compared with conventional parenteral or topical therapy, over longer periods of time than are typical with systemic delivery. Creating cavities or pockets within an organ allows "rebuilding" and reconstruction from inside. Placing therapeutic agents or materials in a "privileged zone," free from overlying blood flow, increases retention and thereby sustains action of the agents. This also provides for more accurate therapy.

Endomural treatment not only localizes the treatment modalities, but also cordons off disease physically, creating barriers to the disease as well as local treatment of the disease.

II. Use of Endomural regions of Organs as Seed Beds

Endomural therapy provides the potential to utilize one organ bed or body as a soil in which to place or plant cells, or organ components to provide another function normally provided by another organ. In many disease states a vital function of an organ is diminished or destroyed by a disease. Conventional therapy aims to pharmacologically limit resultant symptoms or attempt to restore lost function. These approaches are limited. Despite disease of the organ, the remaining tissue components or stroma often have relevant functions themselves. Further, even if specialized tissues and cells of a given organ are diseased, the vascular, neural and stromal matrix of the organ are often intact and are a functional generic organ bed. These residual structures may be looked upon as a fertile "soil" for transplantation or implantation of cells, cell-polymer combinations, other organ components, organoids, artificial organs or bioreactors. These diseased organ shells will function to provide a bed for engraftment of these implants with "housekeeping functions," i.e. arterial and venous supply, lymphatic drainage, innervation, etc., already built-in and intact.

III. Application of Polymeric Structural or Bioactive Materials

As noted above, therapeutic materials such as drugs and cells can be administered and contained intramurally, for treatment of a disease or to provide supplementary function. Other materials, for example, polymers having additional properties such as the ability to facilitate healing, minimize or provoke inflammation, decrease fibrotic response, inhibit abnormal proliferation or other therapeutic benefits, may also be utilized. Polymers may be themselves bioactive or contain embedded or grafted bioactive molecules, peptides, lipids, drugs or other moieties. These polymers may either suppress, maintain or stimulate a biological response. The polymers may also serve as tissue glues, adhesives or sealants to isolate tissue zones, creating internal barriers. These polymers may also serve to provide an artificial biodegradable or permanent scaffold or stroma for implanted or transplanted cells, fragments or tissues.

IV. How to access organ

An organ or tissue can be accessed surgically, either by open exposure or using minimally invasive techniques; or percutaneously.

The endomural regions of an organ or tissue can also be accessed surgically, through open exposure of internal organs or though trans-body wall incisions. This is typically followed by defined focused narrow puncture of the organ, without open radical dissection, and subsequent entry into the endomural zone and placement of a therapeutic.

Endoluminal entry is typically achieved via the use of needles, trocars, ballistic transfer – explosive bullet-like, spark projection, projectile pellets e.g. gene gun, pneumatic transfer (high pressure air, CO_2), chemical permeation, optical or other irradiation-based penetration, ultrasound, electroporation or pheresis –mediated transfer.

These routes and means of penetration are minimally invasive, may be used via direct tissue contact or through key-hole or other limited port entry into the inner aspects of the body, with subsequent defined focused contact and similar penetration means or through subsequent narrow or limited physical puncture of the organ, without open radical dissection, and subsequent entry into the endomural zone for placement of a therapeutic either directly or through the above limited penetration, permeation or other transport means.

Figures 3-5 demonstrate devices which may be used for this purpose. Figure 3A shows a simple balloon device, wherein the catheter 10 includes a balloon 12 permeable to the drug particles 14 to be delivered. An activating or propelling agent or other means 16 within the balloon 12 is used to propel the drug particles 14 out of the balloon 12 and into the tissue as shown in Figure 3B. Figure 3B shows a blood vessel 18 wherein the drug particles 14 have become embedded within the endomural zone 20.

In another embodiment shown in Figure 4A, drug particles 14 can be delivered to a desired location within the endomural zone by introducing a catheter 22 into the tissue lumen, wherein the catheter22 has two expansile members 24 and 26, typically balloons, and means 28 for delivering the drug

particles 14 at a space between the two members 24 and 26; expanding the expansile members 24 and 26 to occlude the targeted portion of the lumen, administering the drug particles 14 by administering a force via an actuator means 30 that propels the drug particles 14 through a macroporous membrane 32 and into the endomural zone, contracting the expansile members 24 and 26, and removing the catheter 22. In one preferred embodiment, the catheter is also used to wash out the occluded region so that, in the case of a blood vessel, the region is substantially free of blood. Figure 4B is an expanded view of the actuator means 30, with expandable walls 32, a tip 34 to insert the actuator means into the delivery means 28, and propellent means 36. The propellent means 36 can be an explosive, hydraulic, or other energy generating means.

As shown in Figure 5A, the drug particles can be delivered using other means, such as a piezoelectric pump 40. The pump 40 includes a nozzle 42 which is rotatable as well as capable of being angled to deliver drug to the appropriate target. This is attached to a catheter 44 including a proximal balloon, distal balloon, guide wire (or other steering means) 46, and, optionally, means 48 for dispersing one or more other materials (including washing or irrigation fluids, adhesive or polymer solutions), etc. and optionally conductive means for heating materials 50, as shown in Figure 5B.

Delivery can also be via a percutaneous route, for example, through transcutaneous entry into conduit systems or "highways" of the body. One advances to the desired region of interest under direct visual guidance, fluoroscopy or ultrasonic guidance, with subsequent entry into the endomural and/or endoluminal zones and placement of a therapeutic, as necessary as outlined above.

Implantable devices or delivery means can include sensors for data measurement, and/or data analyzers, and/or data storage means, and/or data telemetry/transmission means including means for communication at mutiple levels of isolated or nested levels of information transfer. These devices may have incorporated means for modification of the implant or mounting a

response, e.g. local or systemic drug delivery, in response to measurements made using the sensors. These are particularly useful in urology, hepatology or cardiology, where the implants contain one or more sensors responsive to variables which change over time, for example, pressure which is indicative of changes in fluid flow and diameter of the ureter, biliary duct or vessel in which the implant has been placed. Feedback from the sensor(s) either directly, or indirectly via monitoring means external to the patient, signal changes that may be required, such as expansion of the implant in the case where the tissue lumen diameter changes over time or the implant becomes unstable or migrates. In another embodiment, the implant contains a bioactive, prophylactic, diagnostic or pH modifying agent. In one embodiment, the implant is formed of a temperature or pH responsive material so that the agent is released when the temperature or pH is altered.

These systems can also be used to connect a patient to a remote data storage or manipulation system, such as a watch-like device, small portable device, intra or extradermal implant, phone system devices (portable phones, answering services, beepers, office fax machines), portable computer, personal digital assistant (PDA, e.g., Palm Pilot™ systems), or to the internet (world wide web) or a computer accessible through devices that the physician or nurse can monitor or use to interact remotely with the implant.

V. How to create repository zones in organ

Voids may be created via simple catheter, trochar or needle insertion. The void may be of identical size to the insertion device. Alternatively, the void may be made larger via expansile cutter systems which fan-out in a radial or conical or other geometric shape way. Voids may also be created via other mechanical means, e.g. tissue morcellator, balloon dilator, mechanical tissue jack or stretcher, thermal, electrical, ultrasonic laser, UV, x-ray, or other injurious or ablative electromagnetic radiation, cryogenic, chemical – e.g. acids. alkali, detergents, osmotic fragility means, or enzymatic means, e. g. papain, trypsin, chymotrypsin, matrix metalloproteinases, fibrolytic agents,

streptokinase, and tissue plasminogen activator. Aspiration, perfusion or superfusion may be used to further wash and expand the voids.

Voids may be filled with drugs, polymers, polymer-drug mixtures or covalently linked drug-polymer combinations. Polymers may be utilized to further facilitate void creation via delivery of void forming agents, to fill an initially created void for therapeutic purposes, to deliver subsequent therapeutic agents in a tiered or sequenced therapeutic scheme, to limit further void expansion, to provide a neomatrix or scaffold for subsequent cell or tissue engraftment or to form a void- or cavity-barrier limiting void entry or exit. Further, these barriers may be selectively permeable in either a unidirectional or bi-directional fashion.

Polymers may be therapeutic or serve as the means for delivering therapeutic agents. Polymers may be inserted in simple spaces created via device insertion or in larger spaces created as a result of initially creating tissue defects, voids or other cavities. Voids created as a result of disease, defect or surgical procedure are filled with adhesive polymers that facilitate void cavity wall bonding and healing. Polymers are specifically selected to minimize inflammation, secondary bleeding and late fibrotic scarring. Alternatively if an angiogenic or fibrogenic response is desired, polymers may be selected so as to induce a pro-inflammatory, angiogenic, fibrogenic response.

Tissue voids within an organ can be filled with biocompatible biodegradable polymers to act as intra-void tissue bonding agents, allowing collapse and exclusion of the void space while simultaneously increasing intramural lumen space. The polymers may either spontaneously solidify or they may be polymerized or bound to the tissue upon exposure to an appropriate stimulus, as discussed in more detail below. Polymer may posses "therapeutic' hygroscopic or hydrophobic properties to either facilitate progressive water uptake and void shrinkage or to prevent uptake allowing tissue swelling. The polymers are selected to facilitate healing, with minimal inflammatory and late fibrotic responses. Coordinating use of tissue friendly biodegradable polymeric

bioadhesives insures frank volume reduction and obliteration of cavities formed via direct tissue excision. Furthermore, the polymeric materials having drugs, genes or cells incorporated therein may serve as local depots for prolonged delivery of synergistic biochemical and cellular therapeutics, for example, to promote healing, decrease inflammation and/or collagen deposition and scarring, and manipulate endocrine processes and local growth control.

VI. How to implant in the organ

These materials can be implanted in the organ directly, in repository zones, created as described above. Materials to be implanted other than drugs and polymers include cells. Cells can be grown *in vitro*, in cell culture or obtained by biopsy. Cells may be genetically modified. Cells may be isogeneic, allogenic or xenogeneic. Allogenic or xenogeneic cells may be encapsulated for immunotolerance.

Cells may be added as single cells, slurries of single or multiple cell types or from multiple sources, organ fragments or tissue shards. Cells added to a given organ or organ component may be identical or similar differentiated normal cells, different differentiated normal cells, progenitor cells, genetically transfected, transformed or engineered cells, stem cells, embryonic cells, multipotential cells, primordial cells, allogeneic, heterogeneic, xenograft cells, encapsulated allogeneic, heterogeneic, or xenograft cells. Therapeutic non-mammalian, eukaryotic, plant or prokaryotic cells may be delivered.

Therapeutic biologicals such as cell fragments, heterokaryons, viruses, pseudovirions, viroids, prions, DNA, or RNA (sense, antisense, ribozymes or aptemers) may be co-delivered.

Plant cells, prokaryotic cells, or artificial cells may be administered as therapeutically indicated as well. These cells may be passivated or encapsulated to facilitate seeding and routing and to prevent immunorejection.

Cells or tissues from different organs may be transplanted from one organ to function as a substitute in another organ. For example, one could transplant splenocytes into a liver shell or scar or myocardial scar to act as

angiogenic precursors. One could transplant neural stem cells or dorsal root ganglion cells into the heart of patients with diabetes to return sensation of angina as a therapeutically beneficial return of a clinical warning sign. One could transplant splenocytes into bone marow to act as hematologic precursors.

VI. Polymeric or Hydrogel Materials

Biodegradable and/or biocompatible materials may be used to fill, shape, bulk or adhere to voids, cavities, channels or other spaces created by the endomural therapeutic devices to enhance healing, to provide structural support within the cavity, tubular organ or organ component a to assist or obviate the need for other lumen or cavity support following surgery, and/or for drug delivery. For example, polymeric or hydrogel materials can be applied at the surface of or interior of cavities created by removal of tissue to treat the disorders caused by overproliferation or inflammation of tissue. These materials can be used to adhere the sides of the tissue cavity together, to form a barrier at the surface of one or more of the tissue surfaces (to minimize inflammatory processes, for example), for delivery of bioactive agents, for the retention of radioisotopes, radioopaque particulate etc. The polymer may be deployed in the interior of the endomural tissue of the vessel or organ from the surface or tip of the catheter, as discussed above. Alternatively, the polymer can be applied by spraying, extruding or otherwise internally delivered via a long flexible tubular device consisting of as many lumens as a particular application may dictate.

Preferably, the method utilizes biodegradable or bioerodible synthetic or natural polymers, with specific degradation, lifespan and properties, which can be applied in custom designs, with varying thicknesses, lengths, and three-dimensional geometries (e.g. spot, stellate, linear, cylindrical, arcuate, spiral 8, etc.). The pharmaceutical delivery function of the process may be readily combined with the "customizable" deployment geometry capabilities to accommodate the interior of a myriad of complex organ or vessel surfaces. For example, polymer can be applied in either single or multiple polymer layer

configurations and different pharmacological agents can be administered by application in different polymer layers when multiple polymer layers are used.

1. Selection of Polymeric Materials

A variety of different materials can be used, depending on the purpose, for example, structural, adhesive, barrier, or drug delivery. For those applications where structure is required, a polymer is selected which has appropriate mechanical and physical properties. It is preferred that the polymer be biodegradable over a period of time required to heal and form the tissue as desired according to the application. This may be a few days, weeks, or months. An advantage of the polymeric materials is that they can be tailored to shape the polymer into uneven surface interstices, while maintaining a smooth surface with good flow or other tissue compatibility characteristics. Tissue narrowing, if it does occur, tends to stabilize beyond the six month window following the initial procedure without further accelerated narrowing. Optimally, if a foreign support device or sealant material is to be introduced into the tissue, it needs to exert its intended effect principally during the period of healing and peak inflammatory reaction. Although described herein principally with reference to polymeric materials, it is to be understood that other materials may also be used. For example, relatively low molecular weight organic compounds such as common sugars (e.g. sucrose), which are cast from concentrated, warm aqueous solution to set up as monolithic solids *in situ* and erode with minimal swelling or fragmentation may be used in place of a polymeric material. Inorganic compounds formed by ion exchange, such as polysilicic acid salts, degradable bioceramics, and "plasters" which degrade by surface erosion but which set *in situ* can also be used.

For those applications where the purpose does not require structural support properties, the polymer may be formed of a material that is bioadhesive, or impermeable to molecules of specified molecular weights, or highly permeable, releasing incorporating drug over a desired period of time, and consist of as little as a single layer of polymer.

Accordingly, the nature of the polymeric material used will be determined by whether it functions as a coating, bandage, adhesive, drug delivery device, or mechanical support role. Further, the choice of polymer must appropriately balance the degree of structural and geometric integrity needed against the appropriate rate of biodegradation over the time period targeted to prevent an undesirable reaction. In some cases, the material may be the same for different purposes where the ultimate *in vivo* geometry of the polymer dictates the final function of the polymer coating. The thinner applications allow the polymer film to function as a coating, sealant and/or partitioning barrier, bandage, and drug depot. Complex internal applications of thicker layers of polymer may actually provide increased structural support and, depending on the amount of polymer used in the layer, may actually serve in a mechanical role to maintain vessel or organ patency. For example, lesions of tissues that are comprised mostly of fibromuscular components have a high degree of visco-elastic recoil. These lesions or tissues require using the process to apply an endomural coating of greater thickness or stiffness and extent so as to impart more structural stability thereby resisting vessel radial compressive forces. This provides structural stability and is generally applicable for the maintenance of the intraluminal geometry of all tubular biological organs or substructure.

The basic requirements for the polymeric material are biocompatibility and the capacity to be applied in a solid or fluent state then chemically or physically reconfigured under conditions which can be achieved *in vivo* to yield a non-fluent polymeric material having defined characteristics in terms of mechanical strength, permeability, adhesion, and/or release of incorporated materials.

The polymeric materials can be applied as polymers, monomers, macromers or combinations thereof, maintained as solutions, suspensions, or dispersions, referred to herein jointly as "solutions" unless otherwise stated. Polymeric materials can be thermosettable, thermoplastic, polymerizable in response to free radical or ioin formation such as by photopolymerization,

chemically or ionically crosslinkable (i.e., through the use of agents such as glutaraldehyde or ions like calcium ions). Examples of means of solidifying or polymerizing the polymeric materials including application of exogenous means, for example, application of light, ultrasound, radiation, or chelation, alone or in the presence of added catalyst, or by endogenous means, for example, a change to physiological pH, diffusion of calcium ions (e.g., alginate) or borate ions (e.g., polyvinyl alcohol) into the polymeric material, or change in temperature to body temperature (37°C.).

Although either non-biodegradable or biodegradable materials can be used, biodegradable materials are preferred. As used herein, "biodegradable" is intended to describe materials that are broken down into smaller units by hydrolysis, oxidative cleavage or enzymatic action under in vivo conditions, over a period typically less than one year, more typically less than a few months or weeks. For application to tissues to prevent inflammation, enlargement and/or overproliferation, it is preferred to use polymers degrading substantially within six months after implantation. For prevention of adhesions or controlled release, the time over which degradation occurs should be correlated with the time required for healing, i.e., generally in excess of two weeks but less than six months.

Suitable materials are commercially available or readily synthesizable using methods known to those skilled in the art. These materials include: soluble and insoluble, biodegradable and nonbiodegradable natural or synthetic polymers. These can be hydrogels or thermoplastics, homopolymers, copolymers or blends, natural or synthetic. As used herein, a hydrogel is defined as an aqueous phase with an interlaced polymeric component, preferably with 90% of its weight as water. The following definition is from the Dictionary of Chemical Terms, 4th Ed., McGraw Hill (1989): Hydrogel: a colloid in which the disperse phase (colloid) has combined with the continuous phase (water) to produce a viscous jellylike product, for example, coagulated silicic acid. An organogel is defined as an organic phase with an interlaced polymeric

component, preferably with 90% of its weight as organic solvent. Preferred solvents include non-toxic organic solvents, such as dimethyl sulfoxide (DMSO), and mineral and vegetable oils. The preferred polymers are synthetic polymers, formable or synthesizable *in situ*, with controlled synthesis and degradation characteristics.

Representative natural polymers include proteins, such as zein, modified zein, casein, gelatin, gluten, serum albumin, or collagen, and polysaccharides, such as cellulose, dextrans, hyaluronic acid, polymers of acrylic and methacrylic esters and alginic acid. These are not preferred due to higher levels of variability in the characteristics of the final products, as well as in degradation following administration. Synthetically modified natural polymers include alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, and nitrocelluloses, acrylic or methacrylic esters of above natural polymers to introduce unsaturation into the biopolymers.

Representative synthetic polymers include polyesters, polyphosphazines, poly(vinyl alcohols), polyamides, polycarbonates, polyalkylenes, polyacrylamides, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polysiloxanes, polyurethanes and copolymers thereof. Other polymers include celluloses such as methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethyl cellulose, cellulose triacetate, cellulose sulfate sodium salt, acrylates such as poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), polyethylene, polypropylene, poly(ethylene glycol), poly(ethylene oxide), poly(vinyl acetate), polyvinyl chloride, polystyrene, polyvinyl pyrrolidone, and polyvinylphenol. Representative

bioerodible polymers include polylactides, polyglycolides and copolymers thereof, poly(hydroxy butyric acid), poly(hydroxyvaleric acid), poly(lactide-co-caprolactone), poly[lactide-co-glycolide], polyanhydrides, polyorthoesters, blends and copolymers thereof.

These polymers can be obtained from sources such as Sigma Chemical Co., St. Louis, MO., Polysciences, Warrenton, PA, Aldrich, Milwaukee, WI, Fluka, Ronkonkoma, NY, and BioRad, Richmond, CA. or else synthesized from monomers obtained from these suppliers using standard techniques.

These materials can be further categorized as follows.

Materials which polymerize or alter viscosity as a function of temperature.

Poly(oxyalkene) polymers and copolymers such as poly(ethylene oxide)-poly(propylene oxide) (PEO-PPO) copolymers, and copolymers and blends of these polymers with polymers such as poly(alpha-hydroxy acids), including but not limited to lactic, glycolic and hydroxybutyric acids, polycaprolactones, and polyvalerolactones, can be synthesized or commercially obtained. For example, polyoxyalkylene copolymers are described by U.S. Patent Nos. 3,829,506; 3,535,307; 3,036,118; 2,979,578; 2,677,700; and 2,675,619, the teachings of which are incorporated herein. Polyoxyalkylene copolymers are sold by BASF and others under the tradename PluronicTM. Preferred materials include F-127, F-108, and for mixtures with other gel materials, F-67. These materials are applied as viscous solutions at room temperature or lower which solidify at the higher body temperature. Another example is a low Tm and low Tg grade of styrene-butadiene-styrene block copolymer from Polymer Concept Technologies, C-flexTM. Polymer solutions that are liquid at an elevated temperature but solid at body temperature can also be utilized. For example, thermosetting biodegradable polymers for in vivo use are described in U.S. Patent No. 4,938,763 to Dunn, et al.

Several divalent ions including calcium, barium, magnesium, copper, and iron are normal constitutents of the body tissues and blood. These ions can be used to ionically crosslink polymers such as the naturally occurring polymers

collagen, fibrin, elastin, agarose, agar, polysaccharides such as hyaluronic acid, hyalobiuronic acid, heparin, cellulose, alginate, curdlan, chitin, and chitosan, and derivatives thereof cellulose acetate, carboxymethyl cellulose, hydroxymethyl cellulose, cellulose sulfate sodium salt, and ethylcellulose. Materials that can be crosslinked photochemically, with ultrasound or with radiation.

Materials that can be crosslinked using light, ultrasound or radiation will generally be those materials which contain a double bond or triple bond, preferably with an electron withdrawing substituent attached to the double or triple bond. Examples of suitable materials include the monomers which are polymerized into poly(acrylic acids) (i.e., Carbopols.TM.), poly(acrylates), polyacrylamides, polyvinyl alcohols, acrylated polyethylene glycols, and ethylene vinyl acetates. Photopolymerization requires the presence of a photosensitizer, photoinitiator or both, any substance that either increases the rate of photoinitiated polymerization or shifts the wavelength at which polymerization occurs. The radiolysis of olefinic monomers results in the formation of cations, anions, and free radicals, all of which initiate chain polymerization, grafting and crosslinking and can be used to polymerize the same monomers as with photopolymerization. Photopolymerization can also be triggered by applying appropriate wavelength to a cyclo-dimerizable systems such as Coumarin and Cinnamic acid derivatives. Alpha-hydroxy acids backbone can be activated to carbonium ion. COOH or SO_3H functionality can be inserted that can be subsequently reacted to amine containing ligands Materials that can be crosslinked by addition of covalent crosslinking agents such as glutaraldehyde.

Any amino containing polymer can be covalently crosslinked using a dialdehyde such as glutaraldehyde, or succindialdehyde. Examples of useful amino containing polymers include polypeptides and proteins such as albumin, and polyethyleneimine. Peptides having specialized function, as described below, can also be covalently bound to these materials, for example, using crosslinking agents, during polymerization.

Polymers with free carboxylic acid or other anionic groups (e.g., sulfonic acid), such as the acrylic acid polymers noted above, can be used alone or added to other polymeric formulations to enhance tissue adhesiveness. Alternatively, materials that have tissue binding properties can be added to or bound to the polymeric material. Peptides with tissue adhesion properties are discussed below. Lectins that can be covalently attached to a polymeric material to render it target specific to the mucin and mucosal cell layer could be used. Useful lectin ligands include lectins isolated from: *Abrus precatroius, Agaricus bisporus, Anguilla anguilla, Arachis hypogaea, Pandeiraea simplicifolia, Bauhinia purpurea, Caragan arobrescens, Cicer arietinum, Codium fragile, Datura stramonium, Dolichos biflorus, Erythrina corallodendron, Erythrina cristagalli, Euonymus europaeus, Glycine max, Helix aspersa, Helix pomatia, Lathyrus odoratus, Lens culinaris, Limulus polyphemus, Lysopersicon esculentum, Maclura pomifera, Momordica charantia, Mycoplasma gallisepticum, Naja mocambique*, as well as the lectins *Concanavalin A, Succinyl-Concanavalin A, Triticum vulgaris, Ulex europaeus* I, II and III, *Sambucus nigra, Maackia amurensis, Limax fluvus, Homarus americanus, Cancer antennarius*, and *Lotus tetragonolobus*.

The attachment of any positively charged ligand, such as polyethyleneimine, polylysine or chitosan to any microsphere or polymeric chain may improve bioadhesion due to the electrostatic attraction of the cationic groups to the net negative charge of the mucus. A surfactant-like molecule bearing positive charge and a hydrophobic core would be compatible with the bilayer membrane. This molecule will distribute its core and the positive charge to minimize energy of interaction and hence will be more tissue adhesive. The mucopolysaccharides and mucoproteins of the mucin layer, especially the sialic acid residues, are responsible for the negatively charged surface layer. Any ligand with a high binding affinity for mucin could also be covalently linked to the polymeric material.

Polymeric materials can also be used as tissue adhesives. In one form, fibrin is used. This has the advantage that it can be formed easily *in situ* using the patient's own fibrinogen, blood or serum, by addition of thrombin and calcium chloride. The materials described above can also be used. Other polymeric tissue adhesives that are commercially available include cyanoacrylate glues, GRF (Gelatin-resorcinol-formaldehyde) and polyethyleneglycol-poly(lactic acid and/or glycolic acid)-acrylates, both of which are applied as liquids and then photopolymerized.

The polymeric material can be designed to achieve a controlled permeability, either for control of materials within the cavity or into the tissue or for release of incorporated materials. There are basically three situations that the polymeric material is designed to achieve with respect to materials present in the lumen: wherein there is essentially passage of only nutrients (small molecular weight compounds) and gases from the lumen through the polymeric material to the tissue lumen surface; wherein there is passage of nutrients, gases and macromolecules, including large proteins and most peptides; and wherein there is passage of nutrients, gases, macromolecules and cells. The molecular weight ranges of these materials are known and can therefore be used to calculate the desired porosity. For example, a macromolecule can be defined as having a molecular weight of greater than 1000 daltons; cells generally range from 600-700 nm to 10 microns, with aggregates of 30-40 microns in size. For passage of cell, the material must possess or develop a macroporous structure.

Formation of Materials which have decreased volume following polymerization

Under certain circumstances it may be useful to produce a polymer *in situ* which occupies a smaller volume than the solution from which it is applied, for example, as an adhesive for the cavity to hold the walls together. The polymerization can be accompanied by "syneresis" or expulsion of water from the polymer, during polymerization. Besides reducing mass of the product, this process may yield porous products that may be desirable for healing. Syneresis occurs when a polymerization reaction occurs with reaction of a large number of

fractional groups per unit volume (high crosslinking density or when dilute solutions of reactants are polymerized and the amount of water in the formulation exceeds the intrinsic swelling capacity of the resulting polymer. The latter may occur, for example, when dilute solutions of PEG-diacrylate are polymerized (e.g., less than or equal to 5% macromer).

VII. Incorporation of Bioactive Agents

A wide variety of bioactive agents can be incorporated into the polymeric material. These can be physically incorporated or chemically incorporated into the polymeric material. Release of the physically incorporated material is achieved by diffusion and/or degradation of the polymeric material; release of the chemically incorporated material is achieved by degradation of the polymer or of a chemical link coupling the bioactive material to the polymer, for example, a peptide which is cleaved *in vivo* by an enzyme such as trypsin, thrombin or collagenase. In some cases, it may be desirable for the bioactive agent to remain associated with the polymeric material permanently or for an extended period, until after the polymeric material has degraded and removed from the site.

In the broadest sense, the bioactive materials can include proteins (as defined herein, including peptides generally construed to consist of less than 100 amino acids unless otherwise specified), saccharides, polysaccharides and carbohydrates, nucleic acids, and synthetic organic and inorganic materials, or combinations thereof.

Specific materials include antibiotics, antivirals, antiinflammatories, both steroidal and non-steroidal, antineoplastics, anti-spasmodics including channel blockers, modulators of cell-extracellular matrix interactions including cell growth inhibitors and anti-adhesion molecules, enzymes and enzyme inhibitors, anticoagulants, growth factors, DNA, RNA antisense, ribozymes, aptamers, and protein synthesis inhibitors, anti-cell migratory agents, anti-proliferative agents, vasodilating agents, and other drugs commonly used for the treatment of injury to tissue. Examples of these compounds include angiotensin converting enzyme

inhibitors, anti-thrombotic agents, prostacyclin, heparin, salicylates, thrombolytic agents, anti-proliferative agents, nitrates, calcium channel blocking drugs, streptokinase, urokinase, tissue plasminogen activator (TPA) and anisoylated plasminogen activator (TPA) and anisoylated plasminogen-streptokinase activator complex (APSAC), GPIIb/IIIA antagonists, colchicine and alkylating agents, growth modulating factors such as interleukins, transformation growth factor .beta. and congeners of platelet derived growth factor, fibroblast growth factor, epidermal growth factor, hepatocyte scatter factor, leptin, monoclonal antibodies directed against growth factors, modified extracellular matrix components or their receptors, lipid and cholesterol sequestrants, matrix metalloproteases (MMPs), collagenase, plasmin and other agents which may modulate tissue tone, function, and the healing response to organ injury post intervention. Additional examples of such compounds include nitric oxide containing, releasing or producing materials, antiproliferatives as well as antioxidants, a number of which are known.

Hormones, especially reproductive or sex homones, may be particularly advantageous to deliver using these materials. It may also be useful to deliver chemotherapeutics such as BCNU, cisplatin, taxol, Actinomycin D, and other cytotoxic agents. Also addition of stress response inducing agents, evoking heat shock or other mammalian stress protein responses may be desired. Agents include organic and inorganic manganese, tin, cadmium compounds, geldanamycin and analogues oxidizing agents e.g. hydrogen peroxide. Further stress response proteins may also be administered. In certain situations inhibitors of these inducers and of the stress response may also be delivered.

Materials such as attachment peptides (such as the FN cell-binding tetrapeptide Arg-Gly-Asp-Ser (RGDS)), selectin receptors and carbohydrate molecules such as Sialyl Le.sup.x, can be used which serve to attract and bind specific cell types, such as white cells and platelets. Materials such as fibronectin, vimentin, and collagen, can be used to non-specifically bind cell types, to enhance healing. Other proteins known to carry functional RGD

sequences include the platelet adhesion proteins fibrinogen, vitronectin and von Willebrand factor, osteopontin, and laminin. Specific RGD peptides are described in U.S. Patent Nos. 4,517,686 to Ruoslahti, et al., 4,589,881 to Pierschbacher, et al., 5,169,930 to Ruoslahti, et al., 5,149,780 to Plow, et al., 4,578,079 to Ruoslahti, et al., 5,041,380 to Ruoslahti, et al., and Pierschbacher and Ruoslahti, J. Biol. Chem. 262(36), 17294-17298 (1987), Mohri, et al., Amer. J. Hem. 37:14-19 (1991), Aumailley, et al., FEBS 291(1), 50-54 (1991), Gurrath, et al., Eur. J. Biochem. 210, 911-921 (1992), and Scarborough, et al., J. Biol. Chem. 268(2), 1066-1073 (1993). Laminin promotes cell adhesion, migration, differentiation, and growth (Kleinman, et al., J. Cell Biochem. 27:317-325 (1985); Kleinman, et al., Biochem. 25:312-318 (1986); Beck, et al., FASEB J. 4:148-160 (1990). The nonapeptide CDPYIGSR promotes cell attachment and migration (Graf, et al., Cell 48:989-996 (1987), Biochem. 26:6896-6900 (1987)). Further studies have shown that YIGSR-containing peptides can inhibit angiogenesis and tumor metastasis (Grant, et al., Cell 58:933-943 (1989), Iwamoto, et al., Science 238:1132-1134 (1987), Sakamoto, et al., Cancer Res. 51:903-906 (1991). Other peptides include PDSGR and IKVAV. Integrins typically bind to cell adhesion proteins via the rather highly conserved sequence Arg-Gly-Asp X (RGDX), where X is variant depending on the particular cell adhesion protein.

Cells to be incorporated include stromal cells and/or fibroblasts or other mesenchymal cells to facilitate closure of tissue voids. Alternatively glandular epithelial cells, either mature, developing, embryonic/fetal or genetically engineered, may be deposited. These may serve to alter regional or systemic physiology through endocrine or paracrine hormone or other mediator release. Further, neural cells, precursors or tissues may be implanted to facilitate reinnervation and or local adrenergic, cholinergic or other neurotransmitter responses.

In a preferred embodiment, a combination of factors and cells are used to induce angiogenesis in the endomural zone or access tract to the zone.

Exemplary angiogenic growth factors include FGF, PDGF, EGF, VEGF, Midkine chemokines, leptins , angiopoeitin, and other growth factors, inflammatory angiogenic polymers or polymer constructs, electoactive or other microinjurious or locally stimulatory polymers. Preferred cells include endothelial cells, EC bone marrow precursor cells, other stems cells smooth muscle cells or precursors, combinations, neural cells or neural stem cells or combinations with above are placed. These are used for example for angiogenesis, myogenesis or myocardial tissue repair in which myocytes – precursor, differentiated, homograft, isograft, allograft or xenograft are placed in the myocardium, with or without polymer adducts or matix protein mixtures, or with neural cells or other adrenerically active or cholinergically active cell types. Means (hard wire or polymer) for electrically driving, pacing, shocking or sensing the neotissue can also be included.

Essentially the same techniques can be used for nerve regeneration or tissue reinnervation by implanting neurons, Schwann cells, astrocytes, glial cells and/or angiogenic precursors. In one embodiment, the nerve cells are administered with polymer matrices, which may include or be formed of bioactive, biodegradable biostable polymers such as polyethyleneglycol polymers, hyaluronic acid, and laminins.

In yet another embodiment, these techniques are used for local endomural delivery of stress response inducing agents or actual stress response proteins. Both physical and chemical stimuli can be used to induce expression of heat shock proteins. The most frequently studied stimuli are heat, oxidants, and heavy metals. Alternatively, or in addition, heat shock proteins can be directly administered to the cells to be treated. Those that are believed to correlate with a response to injury include hsp70, hsp 90 and other cytoplasmic heat shock proteins. Assays to measure the levels of these proteins are well known to those skilled in the art. However, it should be noted that the inducement of heat shock proteins may not be the actual mechanism by which a

beneficial effect is obtained, but merely an indicator that appropriate conditions have been used which result in the desired beneficial effect.

Several reviews of heat shock proteins have been published, including Schlesinger, Heat Shock: from bacterial to man (Cold Spring Harbor, Cold Spring Harbor, NY 1982); Lindquist, Ann. Rev. Biochem. 55:1151-1191 (1986); Pelham, H.R.B., Cell 46, 959-61 (1986); Lindquist and Craig, "The heat-shock proteins" Annu. Rev. Genet. 22:631-677 (1988); Pelham, EMBO J. 8:3171-3176 (1989); Schlesinger J. Biol. Chem. 265:12111-12114 (1990); Kaufmann, Immunol. Today 11:129-137 (1990); Morimoto Cancer Cells 3:295-301 (1991); Nover, "HSFs and HSPs - a stressful program on transcription factors and chaperones." Stress Proteins, and the Heat Shock Response, sponsored by Cold Spring Harbor Laboratory (Cold Spring Harbor, NY USA April 29-May 2, 1991) Nature New Biol. 3:855-859 (1991); and Nover and Scherf "Heat shock protein, in Heat Shock Response (CRC Press, 1991) pp. 41-127.

In most cases, it is possible to physically incorporate the bioactive agent by mixing it with the material prior to application to the tissue surface or within the cavity and polymerization or solidification. The material can be mixed into the monomer solution to form a solution, suspension or dispersion. In another embodiment, the bioactive agent can be encapsulated within delivery devices such as microspheres, microcapsules, liposomes, cell ghosts or psuedovirions, which in themselves affect release rates and uptake by cells such as phagocytic cells.

Bioactive agents can be chemically coupled (conjugated) to the polymeric material, before or at the time of polymerization. Bioactive materials can also be applied to the surface of catheters, trocars, endoscopes, stents or tissue seals or plugs or sensing implants used in the procedures described herein, alone or in combination with the polymeric materials. Catheter and other device or implant bodies are made of standard materials, including metals such as surgical steel and thermoplastic polymers. Occluding balloons may be made from compliant materials such as latex or silicone, or non-compliant materials

such as polyethylene terephthalate (PET). The expansible member is preferably made from non-compliant materials such as PET, (PVC), polyethylene or nylon. The balloon catheter portion may optionally be coated with materials such as silicones, polytetrafluoroethylene (PTFE), hydrophilic materials like hydrated hydrogels and other lubricous materials to aid in separation of the polymer coating. Seals and plugs may be made of structural biodegradable or biostable polymers as listed above or from hydrogels polymerized in situ, polymerized ex vivo and transported locally or dessicated hydrogels or organogels or mixtures of the above. Sernsing/telemetring implants may be made of combinations of polymeric and microeletronic, microchip, MEMS or other semiconductor type components.

Several polymeric biocompatible materials are amenable to surface modification in which surface bound bioactive molecules/ligands exhibit cellular binding properties. These methods are described by Tay, Merrill, Salzman and Lindon in Biomaterials 10, 11-15 (1989). Covalent linkages can be formed by reacting the anhydride or acid halide form of an N-protected amino acid, poly(amino acid) (two to ten amino acids), peptide (greater than 10 to 100 amino acids), or protein with a hydroxyl, thiol, or amine group on a polymer. The amine groups on the amino acid or peptide must be protected before forming the acid halide or anhydride, to prevent self-condensation. N-protection is well known by those skilled in the art, and can be accomplished by use of various protecting groups, such as a carbobenzoxy (CBZ) group. The term "protecting group" as used herein refers to a moeity which blocks a functional group from reaction, and which is cleavable when there is no longer a need to protect the functional group. Examples of functional groups include, but are not limited to, amino, hydroxy, thio, and carboxylate groups. Examples of protecting groups are well known to those skilled in the art. A carboxyl-containing compound can contain various functional groups, such as hydroxy, thio, and amino groups, that can react with an acid halide or anhydride. These functional groups must be protected before forming an acid chloride or anhydride to avoid self-

condensation. After formation of the acid chloride or anhydride, and subsequent reaction with the hydroxyl, thiol, or amino group(s) on another molecule, the protecting group can be removed in a "deprotecting" step. The N-protected amino groups can be deprotected by means known to those skilled in the art. Any hydroxy or thio groups on these compounds must be protected so as not to react with the acid halides or anhydrides. Examples of suitable protecting groups for alcohols include but are not limited to trialkyl silyl groups, benzyl ethers, and tetrahydropyranyl ethers. These groups can be protected by means known to those skilled in the art, and can be subsequently deprotected after the esterification is complete. Examples of protecting groups can be found in Greene, T. W., and Wuts., P; G. M., "Protective Groups in Organic Synthesis 2d Ed., John Wiley & Sons, Inc., pp. 317-318 (1991), hereby incorporated by reference. A method for preparation of acid halide derivatives is to react the carboxylic acid with thionyl chloride, preferably in benzene or toluene with a catalytic amount of DMF. A known method for producing anhydrides is to react the carboxylic acid with acetic anhydride. In this reaction, as acetic acid is formed, it is distilled out of the reaction vessel. Peptides can be covalently bound to the polymeric material, for example, when the polymeric material is a polymer of an alpha hydroxy acid such as poly(lactic acid), by protecting the amine functionality on the peptide, forming an acid halide or anhydride of the acid portion of the polymer, reacting the acid halide or anhydride with free hydoxy, thiol, or amine groups on the polymer, then deprotecting the amine groups on the peptide to yield polymer having peptide bound thereto via esterification, thioesterification, or amidation. The peptide can also be bound to the polymer via a free amine using reductive amination with a dialdehyde such as glutaraldehyde. The ester groups on a polyester surface can be hydrolyzed to give active hydroxy and carboxyl groups. These groups can be used to couple bioactive molecules. Preferably, before converting the active carboxylate group to the acid halide or anhydride form, the active hydroxy group is protected to avoid reaction with the resulting acid halide or anhydride. As a non-limiting

example, the active hydroxy group can be protected as a benzyl ether. The active carboxyl group can then be converted to the acid halide or anhydride, and reacted with a hydroxy or amino group on a second compound to form an ester or amide linkage. The O-protected hydroxy group can then be deprotected.

Coupling agents such as carbodiimides, diisocyanates, or organosilanes can be used to bind polymers, or metals and ceramics to bioactive agents covalently. For example, a metal stent may be treated with an aqueous solution of an aminotrialkoxy silane. These form an amino functional surface which can react with carboxy-functional proteins, for durable attachment or controlled release. Carbodiimides can react with carboxyl functional groups to produce amino-reactive intermediates. Carboxy functional polymers can be reacted to form N-hydroxy succinimide esters which are very reactive with amino groups on peptides. This chemistry has been used to form surgical sealants PEG-di-N-hydroxysuccinimide and albumin, Barrows, et al., 3M Corporation, but could be used to couple bioactive molecules to polymers.

2. Application of Polymeric Materials

In general terms, the polymeric material is a biocompatible polymeric material having a variable degree of fluency in response to a stimulus or mechanical pressure, as described above. The material is such that it is substantially non-fluent *in vivo* upon completion of the coating process. The material, in its fluent form or a conformable form, is positioned in contact with a tissue or device surface to be coated and then stimulated to render it non-fluent or conformed, as described above. The polymeric material is applied to the cavity or endomural void using catheters, syringes, or sprays, depending on the tissue surface or device to which it is applied, using the devices described above or devices known to those skilled in the art.

The coating typically will be applied to a tissue surface such as the media of an artery, the urethra, brain or the myocardium using some type of catheter, trocar or scope. The coating material is preferably applied using a single catheter or similar device with single or multiple lumens. The catheter

should be of relatively low cross-sectional area. A long thin tubular catheter manipulated using endoscopic guidance is preferred for providing access to the interior of organ areas. Alternatively the device may have direct vision capabilities via contained fiberoptics or actual tip cameras (CCD, C-MOS,etc) or via echo sensing, US sensing or GPS positioning systems.

Application of the coating material may be accomplished by extruding a solution, dispersion, or suspension of monomers, polymers, macromers, or combinations thereof through a catheter to coat or fill a tissue surface or cavity, then controlling formation of the coating by introducing crosslinking agents, gelling agents or crosslinking catalysts together with the fluent material and then altering the conditions such that crosslinking and/or gelling occurs. Thus, when a balloon catheter is used, a flow of heated or chilled fluid into the balloon can alter the local temperature to a level at which gelling or cross-linking is induced, thereby rendering the material non-fluent. Localized heating or cooling can be enhanced by providing a flow of heated or chilled liquid directly onto the treatment site. Thermal control can also be provided, however, using a fluid flow through or into the balloon, or using a partially perforated balloon such that temperature control fluid passes through the balloon into the lumen. Thermal control can also be provided using electrical resistance heating via a wire running along the length of the catheter body in contact with resistive heating elements. This type of heating element can make use of DC or radio frequency (RF) current or external RF or microwave radiation. Other methods of achieving temperature control can also be used, including light-induced heating using an internal optical fiber (naked or lensed). Altrnatively as self-contained fluid flow system allowing inflow and outflow of fluids to the ballon, actuator or other material applying tip of surface may control polymer flow, melt, setup and cooling and fixation. The polymer formulation can contain components which convert light into heat energy. Similar devices can be used for application of light, ultrasound, or irradiation.

Alternatively the polymers may be delivered as solid materials of various configurations e.g. rods, speheres, folded sheets, yarms, meshes, twines, ropes, particles , amorphous shapes, flakes, etc. Similarly hydrogel materials may be dlivered with the above physical geometries in either the hydrated, partially hydraed or dessicated form. Further defined hydrogel shapes shuch as spikes, spheres with wicks and other tract + void shapes may be delivered for the purpose of void sealing or plugging or repair.

Any of the foregoing materials can be mixed with other materials to improve their physiological compatibility. These materials include buffers, physiological salts, conventional thickeners or viscosity modifying agents, fillers such as silica and cellulosics, and other known additives of similar function, depending on the specific tissue to which the material is to be applied.

The process of fixing the shape of the polymeric material can be accomplished in several ways, depending on the character of the original polymeric material. For example, a partially polymerized material can be expanded using a balloon after which the conditions are adjusted such that polymerization can be completed, e.g., by increasing the local temperature or providing UV or visible radiation through an optical fiber. A temperature increase might also be used to soften a fully polymerized sleeve to allow expansion and facile reconfiguration and local molding, after which it would "freeze" in the expanded position when the head source is removed. Of course, if the polymeric sleeve is a plastic material which will permanently deform upon stretching (e.g., polyethylene, polyethylene terephthalate, nylon or polyvinyl chloride), no special fixation procedure is required.

The present invention will be further understood by reference to the following non-limiting examples.

Example 1: Application of tissue adhesive in a cavity.

An incision in an organ is made. A tissue adhesive is then applied within the cavity to enhance healing of the wound. The following are examples of useful tissue adhesives to close the voids.

a. 1 gm of 50 mg Fibrinogen/ml is mixed in situ with 0.3 g of 150 NIH U thrombin/ml containing 100 mM $CaCl_2$ at the site of the cavity. This forms a tissue glue within 90 sec.

b. 2 gm of 100 mg Fibrinogen/ml is mixed in situ with 0.3 g of 150 NIH U thrombin/ml containing 100 mM $CaCl_2$ at the site of the cavity. This forms a tissue glue within 30 sec.

c. 1 gm of 50 mg Fibrinogen/ml is supplemented with 2500 kIU Aprotinin/ml with 12.5 mg epsilon-aminocaproic acid/ml. The solution is mixed *in situ* with 0.3 g of 150 NIH U thrombin/ml containing 100 mM $CaCl_2$ at the site of the cavity. This will delay the *in vivo* degradation of Fibrin glue and retain the collapsed state of the cavity for a longer duration of time. Tranexamic acid can be used instead of aprotinin for better healing response of the tissue.

Example 2: Dehydration of tissue before application of glue.

In another example, a cavity is aspirated following washing with a concentrated ethanol solution (80% w/w in water). This process dehydrates the local area of the cavity. The in situ Fibrin glue is applied as described above to promote better adhesion of the tissue.

Modifications and variations of the methods and compositions described above will be obvious to those skilled in the art and are intended to be encompassed by the following claims.

We claim:

1. A method of treatment comprising locally penetrating and entering the body of an organ, organ component or tissue structure with minimal damage to obtain access to endomural zones of an organ.

2. The method of claim 1 further comprising depositing in the midzone therapeutic agents and systems.

3. The method of claim 2 wherein the therapeutic agents are selected from the group consisting of drugs, cells and polymers and diagnostic and/or therapeutic devices.

4. The method of claim 3 wherein the polymers may be degradable or non degradable.

5. The method of claim 3 wherein the polymers are selected from the group consisting of solid matrices, porous matrices, hydrogels, organogels, colloidal syspensions, microparticles and microcapsules, anoparticles and combinations therof.

6. The method of claim 3 wherein the drugs are selected from the group consisting of anti-infectives, antibiotics, antifungal, antihelminthic, antiparasistic agents, anticancer agents, anti-proliferative agents, anti-migratory agents, anti-inflammatory agents, metalloproteases, proteases, thromblytic agents, fibrinolytic agents, steroids, hormones, vitamins, charbohydrates, lipids proteins, peptides and enzymes.

7. The method of claim 3 wherein the drugs are proliferative growth factors selected from the group consisting of PDGF, FGF, TGF, EDGF, Epidermal GF, NGF, ILGF, Hepatocyte scatter factor, angiogenic growth factors, serum factors, collagen, laminin, tenascin, SPARC, thrombospondin, fibronectin, vimentin and other matrix factors.

8. The method of claim 3 wherein the cells are selected from the group consisting of autogenous similar cells (i.e. mesenchymal for mesenchymal) from adjacent normal zones of the same or different organs.

9. The method of claim 3 wherein the cells are selected from the group consisting of autogenous differing cells (i.e. mesenchymal for ectodermal or splenocytes for endothelial cells) from adjacent normal zones of the same or different organs.

10. The method of claim 3 wherein the cells are therapeutic factors produced by or in the form of stem cells or other progeneitor cells.

11. The method of claim 3 wherein the cells are explanted and clonally or otherwise expanded *in vitro* for implantation, either without genetic modification or genetically modified, before implantation.

12. The method of claim 3 wherein the therapeutic factors are selected from the group consisting of genes, plasmids, episomes, viruses, viroids, or other microorganisms for therapeutic or synthetic purpose.

13. The method of claim 3 wherein the therapeutic factors are heat shock or stress response proteins or inducers of heat shock or stress response proteins.

14. The method of claim 1 further comprising where a cavity or containment space or reservoir area does not exist in the endomural zone, creating such a space for therapeutic placement.

15. A device comprising a hollow tubular member with an end penetrating or cuting means causing minimal collateral damage and means for delivery of therapeutic agents into endomural tissue.

16. The device of claim 15 wherein the member is rigid made of metal, polymer, or composite.

17. The device of claim 15 wherein the member is flexible and comprises a catheter-like device.

18. The device of claim 15 wherein the member is attached to a single or multiple reservoirs for therapeutic agent containment and delivery.

19. The device of claim 15 wherein the member has an expansile cutter at the distal end to create a tissue space.

20. The device of claim 15 further comprising diagnostic or therapeutic sensors.

21. The device of claim 15 further comprising projectile means to ballistically transfer particles through the ectoluminal or endoluminal zone for retention in the endomural zone.

22. The device of claim 21 wherein the projectile means is selected from the group comprising mechanical acceleration, electrical transfer, spark explosion, and gas explosion.

23. The device of claim 15 further comprising means for indirect or direct guidance means.

24. The device of claim 23 wherein the means for direct guidance is selected from the group consisting of fiber optic imaging systems, endoscopes, direct tip cameras, CCD, C-MOS or other chip or electrical video systems, ultrasound or GPS positioning systems.

25. The device of claim 15 in a kit comprising a void filling material which contains electroactive agents.

26. The device of claim 15 comprising a void filling material or implant which can locally sense, store or telemeter physical, chemical or biological information.

27. The device of claim 15 comprising electoactive or electroconductive polymers which may be directly or externally activated via transcutaneous energy delivery to elicit positive or negative galvanotaxis (tissue healing or cell movement to or from based on local persistent or intermittent electrical current).

28. The device of claim 15 comprising a therapeutic for induction of angiogenesis or myogenesis.

29. The device of claim 28 comprising a therapeutic selected from the group of angiogenic growth factors, inflammatory angiogenic polymers or polymer constructs, electoactive or other microinjurious or locally stimulatory polymers.

30. The device of claim 28 comprising cells selected from the group consisting of endothelial cells, EC bone marrow precursor cells, other stems cells smooth muscle cells or precursors, combinations, neural cells or neural stem cells or combinations with above are placed.

31. The device of claim 15 for nerve regeneration.

32. The device of claim 15 comprising a bioactive polymer.

33. The device of claim 15 comprising stress response inducing agents or actual stress response proteins.

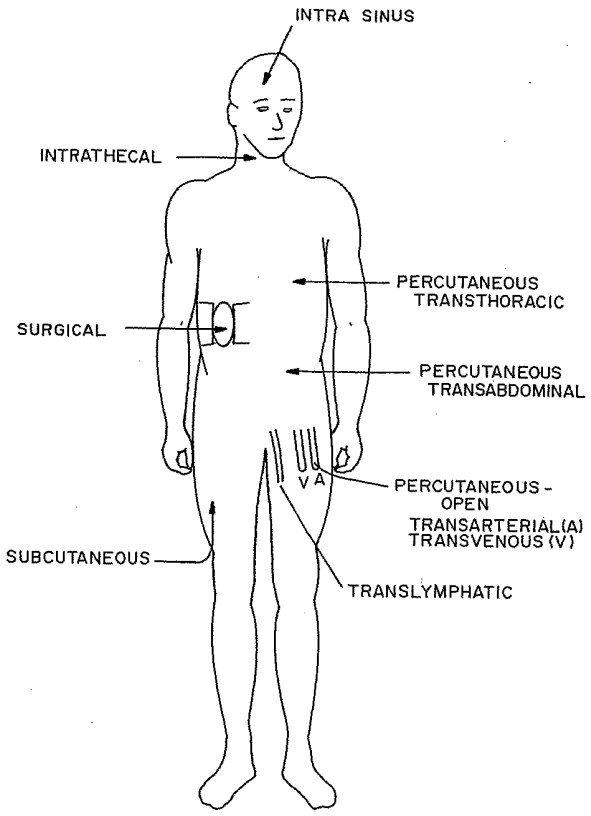

INTRA SINUS
INTRATHECAL
PERCUTANEOUS TRANSTHORACIC
SURGICAL
PERCUTANEOUS TRANSABDOMINAL
V A
PERCUTANEOUS - OPEN TRANSARTERIAL(A) TRANSVENOUS (V)
SUBCUTANEOUS
TRANSLYMPHATIC

FIG. 1

FIG. 2A

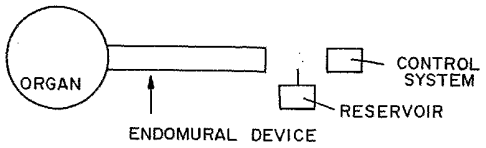


FIG. 2B

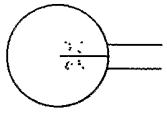


FIG. 2E

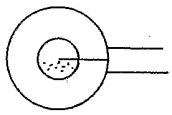


FIG. 2C

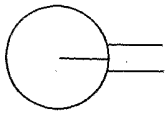


FIG. 2F

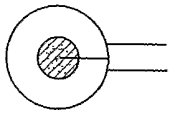


FIG. 2D

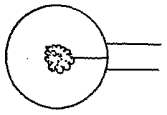


FIG. 2G

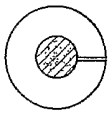


FIG. 3A

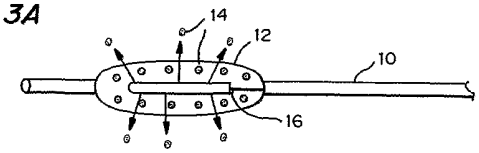


FIG. 3B

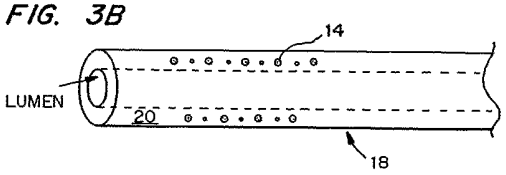


FIG. 4A

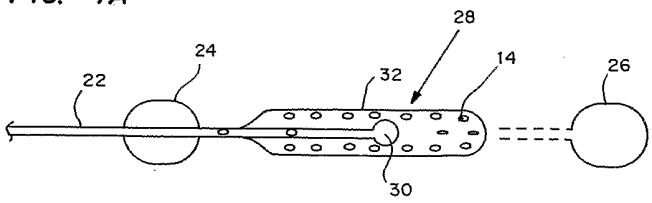


FIG. 4B

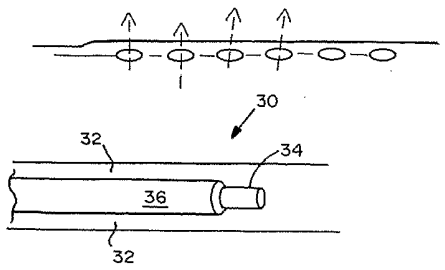


FIG. 5A

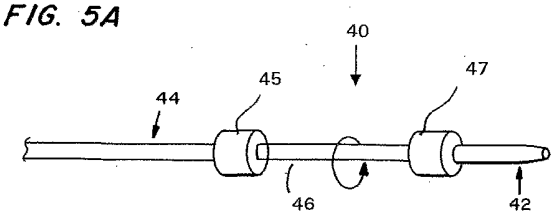
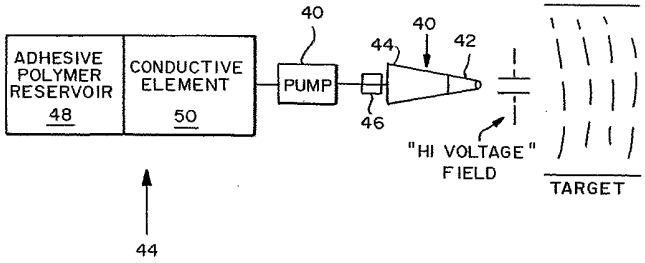

40
45
47
44
46
42

FIG. 5B


ADHESIVE POLYMER RESERVOIR
48
CONDUCTIVE ELEMENT
50
PUMP
40
44
40
42
46
"HI VOLTAGE" FIELD
TARGET
44

フロントページの続き

(51)Int.Cl.[7]	FI	テーマコード（参考）
Ａ６１Ｋ 9/50	Ａ６１Ｋ 9/50	４Ｃ０８７
Ａ６１Ｋ 31/56	Ａ６１Ｋ 31/56	４Ｃ１６７
Ａ６１Ｋ 35/12	Ａ６１Ｋ 35/12	
Ａ６１Ｋ 35/24	Ａ６１Ｋ 35/24	
Ａ６１Ｋ 38/00	Ａ６１Ｋ 45/00	
Ａ６１Ｋ 38/16	Ａ６１Ｋ 47/30	
Ａ６１Ｋ 38/17	Ａ６１Ｍ 37/00	
Ａ６１Ｋ 38/22	Ａ６１Ｐ 9/10	
Ａ６１Ｋ 38/43	Ａ６１Ｐ 35/00	
Ａ６１Ｋ 45/00	Ａ６１Ｋ 37/24	
Ａ６１Ｋ 47/30	Ａ６１Ｋ 37/02	
Ａ６１Ｍ 37/00	Ａ６１Ｋ 37/48	
Ａ６１Ｐ 9/10	Ａ６１Ｋ 37/12	
Ａ６１Ｐ 35/00	Ａ６１Ｋ 37/04	

(81)指定国 AP(GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZM,ZW),EA(AM,AZ,BY,KG,KZ,MD,RU,TJ,TM),EP(AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE,TR),OA(BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG),AE,AG,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,EC,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,MZ,NO,NZ,OM,PH,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TN,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZM,ZW

(72)発明者 スレピアン, マーヴィン ジェイ.
アメリカ合衆国 アリゾナ ８５７５０, タクソン, ノース サミット リッジ ロード ５００１

Ｆターム(参考) 4C060 MM21 MM24
4C076 AA08 AA16 AA30 AA61 CC03 CC04 CC11 CC14 CC27 CC31 CC32 CC34 EE01A FF02
4C081 AC08 BB07 CE02 CE11 DA03
4C084 AA02 AA17 DA40 DB01 DB53 DB54 DB55 DB57 DB59 DC02 DC09 DC35 DC50 MA23 MA28 MA38 MA41 MA63 MA70 NA10 ZA451 ZB261
4C086 AA01 DA08 MA02 MA05 MA28 MA38 MA43 MA63 NA10 ZA45 ZB26
4C087 AA01 BB63 CA04 MA23 MA28 MA38 MA43 MA63 NA10 ZA45 ZB26
4C167 AA02 AA75 BB42 BB62 CC06 GG16 GG21

专利名称(译)	<无法获取翻译>		
公开(公告)号	JP2004533277A5	公开(公告)日	2005-12-22
申请号	JP2002563816	申请日	2002-02-08
[标]申请(专利权)人(译)	结束管腔Therapeutics公司		
申请(专利权)人(译)	Endoruminaru Therapeutics公司		
[标]发明人	スレピアンマーヴィンジェイ		
发明人	スレピアン, マーヴィン ジェイ.		
IPC分类号	A61B17/00 A61B17/34 A61K9/00 A61K9/06 A61K9/10 A61K9/14 A61K9/50 A61K31/56 A61K35/12 A61K35/24 A61K38/00 A61K38/16 A61K38/17 A61K38/22 A61K38/43 A61K45/00 A61K47/30 A61L27/00 A61M25/00 A61M37/00 A61P9/10 A61P35/00		
CPC分类号	A61K9/0024 A61B17/00491 A61B17/3478 A61B2017/00398 A61B2017/00871 A61M25/00 A61M2025/0057 A61M2025/0058		
FI分类号	A61L27/00 A61B17/00.320 A61K9/06 A61K9/10 A61K9/14 A61K9/50 A61K31/56 A61K35/12 A61K35/24 A61K45/00 A61K47/30 A61M37/00 A61P9/10 A61P35/00 A61K37/24 A61K37/02 A61K37/48 A61K37/12 A61K37/04		
F-TERM分类号	4C060/MM21 4C060/MM24 4C076/AA08 4C076/AA16 4C076/AA30 4C076/AA61 4C076/CC03 4C076/CC04 4C076/CC11 4C076/CC14 4C076/CC27 4C076/CC31 4C076/CC32 4C076/CC34 4C076/EE01A 4C076/FF02 4C081/AC08 4C081/BB07 4C081/CE02 4C081/CE11 4C081/DA03 4C084/AA02 4C084/AA17 4C084/DA40 4C084/DB01 4C084/DB53 4C084/DB54 4C084/DB55 4C084/DB57 4C084/DB59 4C084/DC02 4C084/DC09 4C084/DC35 4C084/DC50 4C084/MA23 4C084/MA28 4C084/MA38 4C084/MA41 4C084/MA63 4C084/MA70 4C084/NA10 4C084/ZA451 4C084/ZB261 4C086/AA01 4C086/DA08 4C086/MA02 4C086/MA05 4C086/MA28 4C086/MA38 4C086/MA43 4C086/MA63 4C086/NA10 4C086/ZA45 4C086/ZB26 4C087/AA01 4C087/BB63 4C087/CA04 4C087/MA23 4C087/MA28 4C087/MA38 4C087/MA43 4C087/MA63 4C087/NA10 4C087/ZA45 4C087/ZB26 4C167/AA02 4C167/AA75 4C167/BB42 4C167/BB62 4C167/CC06 4C167/GG16 4C167/GG21		
代理人(译)	夏木森下		
优先权	60/267578 2001-02-09 US		
其他公开文献	JP2004533277A		

摘要(译)

单独的聚合物材料或与生物活性剂或细胞组合的聚合物材料尤其可用于开放式外科手术应用，微创或经皮应用，经粘膜应用，在所开发的医疗应用中用于治疗或修复，替换，移植或增强组织的装置和方法它完成了。这些方法和装置可用于修复，改变或增强实体器官或管状结构的中心或壁内方面的功能。在一个实施方案中，本发明的方法还包括在中间区域中沉积治疗剂和治疗系统。