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(54) SYSTEM FOR TREATMENT AND IMAGING USING ULTRASONIC ENERGY AND MICROBUBBLES

SYSTEM ZUR BEHANDLUNG UND BILDDARSTELLUNG MIT ULTRASCHALLENERGIE UND MIKROBLÄSCHEN

SYSTÈME POUR LE TRAITEMENT ET L'IMAGERIE UTILISANT L'ÉNERGIE ULTRASONORE ET DES MICROBULLES

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Description

BACKGROUND OF THE INVENTION

[0001] Cardiovascular disease (CVD) was blamed for 37% of the 2.4M deaths in the US (2003) [I]. CVD is the leading cause of death in the US and the developed world.

Currently available drug-eluting stents (PES) pose a major potential health concern

[0002] The clinical use of Drug Eluting Stents (DES), in relation to Bare Metal Stents (BMS), has evolved over a period of approximately 18 months from approximately 0% usage in the U.S., to the point where they were used in approximately 80% of coronary stent procedures in the U.S. [2, 3].

[0003] The above cited recent studies indicates that there is a significant, growing population (approximately 6 Million individuals worldwide [4]) who currently find themselves having been implanted with DES and face a choice between taking the expensive and risky drug clopidogrel - potentially for life - or increased risk of premature death.

The vascular smooth muscle cell, VCAM-I and rapamycin: Vascular SMC proliferation contributes to angioplasty -induced stenosis and in-stent restenosis.

[0004] The primary function of the vascular SMC in adult animals is contraction and SMCs express a unique repertoire of genes that allow for this specialized form of contraction, including SM α-actin, smooth muscle myosin heavy chain (SMMHC), SM22α, calponin, desmin, smoothelin - genes we refer to as SMC differentiation marker genes [5-8]. This repertoire of genes is typically used to describe the "contractile" phenotype or mature SMC.

VCAM-I is a marker of the phenotypically modified/proliferating SMC.

[0005] The changes in SMC gene expression profiles associated with injury-induced phenotypic modulation are transient. That is, SMCs undergo phenotypic modulation as a natural response to repair the injured blood vessel, transitioning from a contractile phenotype to a synthetic phenotype but revert back to a contractile phenotype as the lesion resolves itself. Thus, this continuum of altered SMC gene expression profiles can be used to target the phenotypically modified SMC that invests in the developing neointima using molecular targeting. VCAM-I (vascular cell adhesion molecule 1) is expressed in proliferating SMCs [9, 10] and transiently upregulated in SMCs following acute vascular injury and in atherosclerotic lesions [H]. The function of VCAM-I is to promote cell-cell interaction required for SMC migration and recruitment or attraction of other cell types into the lesion, e.g. VCAM-I interaction on SMCs with integrins on leukocytes, monocytes or macrophages (all inflammatory cells) [9]. Because VCAM-I is expressed at much lower levels in the quiescent contractile SMC phenotype, but increased in proliferating SMCs, VCAM-I can thus be used to target the proliferating SMC.

Rapamvcin is a potent SMC anti-proliferative agent and the bench-mark agent for preventing in-stent restenosis by release from a PES.

[0006] The cell cycle consists of 5 basic steps: dormancy (GO) or the contractile SMC phenotype, gap phase 1 (GI), synthesis (S), pre-mitosis or gap phase 2 (G2) and mitosis (M). In response to acute vascular injury, SMCs leave GO and enter GI to begin the process of cell proliferation and division into M phase; this is the synthetic migratory or proliferative SMC phenotype. The strategies for preventing SMC proliferation and entry into the cell cycle have been to block various phases of the cell cycle once the cell has left GO in response to injury or some acute growth stimulus. Sirolimus, or rapamycin, and its analogues, ABT578 (Abbot Pharmaceuticals) and everolimus, are immunosuppressants with both anti-inflammatory and antiproliferative properties that interfere early in the cell cycle by inhibiting the passage of cells from GI to S phase. Drugs that inhibit cell cycle in the GI phase are considered cytostatic and may be less toxic than drugs that act later in the cell cycle [12, 13]. Rapamycin is the most thoroughly investigated agent of this group and has become the bench-mark agent for the prevention of coronary artery restenosis [14]. Thus, because rapamycin is considered "*cytostatic*", SMCs treated with rapamycin do not die but maintain their viability in the growth arrested state.

Molecular Targeting of Microbubble Carriers

[0007] Recent research has investigated the feasibility of targeted ultrasound contrast microbubbles as a means of detecting intravascular manifestations of disease. Pathology is often accompanied by alterations of the endothelial cell layer lining of the affected blood vessels. This dysfunction may occur in the microcirculation, and is identified by the selective expression or up-regulation of certain molecules on the vascular endothelial surface. Many of the molecular markers of endothelial dysfunction corresponding to disease states such as atherosclerosis [15], transplant rejection [16], inflammation and ischemia reperfusion injury [17] are well characterized. However, there is currently no non-invasive, clinically approved technique to assess the extent and location of such vascular pathologies. Experimental formulations of targeted microbubbles, which contain a surface-bound ligand specific for the intended target, are injected intra vascularly and, after a short circulation period, are observed to accumulate at the target site. Subsequent ultrasound im-

aging enables determination of the location and extent of the targeted disease state [18]. This technique, known as "targeted contrast enhanced ultrasound", may achieve high spatial resolution, real time imaging, and a linear or other measurable correlation between adherent microbubbles and the received signal.

[0008] Further, from US 5,558,092 A (Unger et. al) a transducer design including therapeutic and imaging array elements with a common front face plane is known. From US 2004/030250 A1 (Stewart), an injection catheter with a piezoelectric ultrasound emitting device at its distal end, capable of emitting ultrasound of different energy levels, is known. Furthermore, from US 2005/084538 A1 (Dayton et. al), methods, compositions and apparatus for localized delivery of compounds are known, in which radiation force may be used to direct carriers to a target site, and additional radiation may be used to fragment the localized carriers, releasing associate compounds. Further, US 2004/059219 A1 discloses an ultrasonic diagnosing/treating device and method.

[0009] There is therefore a need for, among other things, the drug, the drug carrier, and the means of localizing delivery; and a means to guide the focal delivery under real time image guidance.

SUMMARY OF THE INVENTION

[0010] There is a need for real time, noninvasive, imaging method to reliably guide the focal delivery of antiproliferative drug to regions at risk of restenosis following angioplasty and/or stenting.

[0011] The present invention relates to an ultrasound catheter system for providing therapy to a treatment site at one or more locations of a subject according to claim 1. The dependent claims describe examples of such a system.

[0012] Said one or more locations may comprise, for example, a portion of an organ, wherein said organ may, for example, comprise hollow organs, solid organs, parenchymal tissue, stromal tissue and/or ducts. The one or more locations may alternatively or additionally comprise a portion of a tubular structure, wherein the tubular structure may comprise a blood vessel, and wherein the portion of a tubular structure may comprise at least one of the following: stenosis region or any region exhibiting vascular disease. In the examples according to claim 1, said ultrasonic energy may further be adapted for providing ultrasonic radiation forces for translating said microbubbles into or in the vicinity of the treatment site.

[0013] An aspect of some of the various embodiments of the disclosure comprise an ultrasound contrast agent that have a selected drug incorporated into the bubble shell. In one embodiment, the drug may be rapamycin. It should be appreciated that the present invention is not limited to any particular drug or class of drug, or agent (or any other type of medium or material being delivered to the location of the subject or the treatment site or diagnostic site of the subject. The invention further comprises the means (a transducer [or transducer array] and its associated driving electronics) to deliver ultrasound energy ("therapeutic") to break the bubbles in such a manner as to focally deliver drug material to selected local cells. For example, but not limited thereto, the selected cells are those on or in the wall of a selected blood vessel. The precise mechanisms and the optimal conditions for ultrasound mediated drug delivery are heretofore not well understood. What is known from extensive literature is that the combination of bubbles plus ultrasound greatly improve the delivery of drug (or gene) material through the cell membrane. In an approach, the "therapeutic" ultrasound transducer is intimately integrated with an "imaging" ultrasound transducer that provides real-time, noninvasive imaging for guiding the precise delivery of potent drugs to a selected tissue region. Similar transducers used clinically are referred to as intravascular ultrasound (IVUS) catheters. Typically, the design of an optimal imaging transducer and an optimal therapeutic transducer are different - e.g. the therapeutic transducer may operate in a high power transmit mode of about 0.5 to about 2 MHz, whereas the imaging transducer operates as a finely sampled imaging array about 5 to about 30 MHz range. It should be appreciated that other higher and lower frequency modes may, of course, be employed within the context of the disclosure as desired or required. Nevertheless, it is possible to make compromises in the transducer design and arrive at a common design for both imaging and therapeutic effect.

[0014] The combined transducer is catheter-based, may transthoracically-based (i.e. "conventional" diagnostic ultrasound) and intravascularly, as is the case with IVUS - introduced through femoral or carotid artery. The transducer may also be introduced via any natural or synthetic body cavity/orifice (uretha, anus, vagina, mouth/esophagus or surgical incision in any body part). Transducer designs (or aspects thereof) for some of these applications or aspects of the applications may be known in context of conventional diagnostic ultrasound and most large vendors develop and market transducers for each of these applications.

[0015] The drug / contrast may be delivered systemically via intravenous (IV) injection or it may be delivered more locally such as from an aperture / conduit in a catheter placed into the veinous or arterial circulatory system.

[0016] The drug may exist "side by side" with the agent - i.e. the drug not bound into the bubble shell. When the drug is injected "side by side" it may be dissolved in any suitable solvent appropriate for that drug (e.g. water, lipid, alcohol, or solid form-for example, in very fine particle form-like nanoparticle, etc. Moreover, the drug could be in a gas or solid, for example, could be in the core or shell of the bubble (respectively)); in addition to being in the liquid phase, the drug may be used in the solid dosage forms, such as in nanoparticle formulations of kinds familiar to those skilled in the art.

[0017] The bubbles may be molecular targeted to enhance cell-specific selectivity -per the techniques, for ex-

ample, described in the multiple papers by Klibanov [19, 20] and colleagues.

[0018] An aspect(s) of various embodiments of the present disclosure may be provide a number of features, elements and characteristics, such as but not limited thereto, the following: integrated image guidance of ultrasound-based local drug delivery; integrated image guidance of ultrasound-based local gene delivery; cell-specific molecular targeting of therapeutic agent; and ultrasound imaging-based estimation of the delivery of therapeutic agent.

[0019] These and other objects, along with advantages and features of the invention disclosed herein, will be made more apparent from the description, drawings and claims that follow.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] The accompanying drawings, which are incorporated into and form a part of the instant specification, illustrate several aspects and embodiments of the present invention and, together with the description herein, and serve to explain the principles of the invention. The drawings are provided only for the purpose of illustrating select embodiments of the invention and are not to be construed as limiting the invention.

FIG. 1 provide a schematic illustration of an embodiment (or partial embodiment) of the present invention ultrasound catheter system 102 for providing therapy (and/or diagnosis) to a treatment site at one or more locations of a subject.

FIGS. 2(A)-(C) schematically illustrate various embodiments (or partial embodiments) of the present invention ultrasound catheter system for providing therapy (and/or diagnosis) to a treatment site at one or more locations of a subject.

FIGS. 3(A)-(C) schematically illustrate the arrays of the Forsberg array, Bouakaz array, and present invention embodiment array, respectfully.

FIG. 4 schematically illustrate an embodiments (or partial embodiment) of the present invention ultrasound catheter system.

FIG. 5: illustrates the epifluorescence microscopy observations (**FIG**. **5 A, B, C**) and ultrasound backscatter imaging (**FIG**. **5D, E, F**) of adherent microbubbles. Microcapillaries infused with buffer alone show no microbubble adhesion (**A**) and no ultrasound signal (dashed box illustrates microcapillary location) (**D**). Few adherent microbubbles are visible in flow-only microcapillaries (**B**), and the corresponding echo is identifiable but weak. A large number of adherent microbubbles are present in a microcapillary exposed to radiation force at 122 kPa (**C**), and the corresponding echo is strong. Scale bar represents 5 μm.

FIG. 6 illustrates a 10 MHz (e.g., Sequoia CPS) image of mouse common carotid using microbubbles with dual targeting: polymeric sialyl LewisX (psLex) and anti-mouse VCAM-I. Cho et al. "Dual-Targeted Contrast" AHA Abstract 2006. See Weller GE, Villanueva FS, Tom EM, Wagner WR. Targeted ultrasound contrast agents: in vitro assessment of endothelial dysfunction and multi-targeting to ICAM-I and sialyl Lewisx.Biotechnol Bioeng. 2005 Dec 20;92(6):780-8.

FIG. 7 illustrates: at **FIG. 7(A)** a B-Mode of rat carotid (40MHz, Vevo). Yellow arrows point to the blood vessel; at **FIG. 7(B)** a **B**-mode of a rat carotid artery (12 MHz); and at **FIG. 7(C)** 10 MHz ultrasound imaging using bubble sensitive/specific imaging mode. White tracing denotes the carotid artery wall. White Scale bars = 10 mm.

FIG. 8 illustrates prototype pulse echo responses of dual layer (multi-frequency) transducer. **FIG. 8** illustrates: at **FIG. 8(A)** a low frequency layer pulse-echo response; at **FIG. 8(B)** an Experimental high frequency pulse-echo response; at **FIG. 8(C)** an experimental high frequency pulse echo response after inverse filtering; and at **FIG. 8(D)** an FEA simulation of proposed, improved (better acoustic matching) high frequency layer design (without filtering) All plots are voltage echo response vs. time (μs)

FIG. 9 illustrates a diagram of targeted ultrasound contrast microbubble. The gas core is encapsulated by a lipid monolayer shell, which is coated with a PEG brush. The targeting ligand, here an anti-P-selectin monoclonal antibody, is secured to the distal tips of the polymers via a biotin-streptavidin link. Figure is not to scale.

FIG. 10 illustrates a microbubble adhesion at wall shear rate of 355 s-1 on P-selectin after insonation at 122 kPa (122 kPa on P-sel; n=4), adhesion on P-selectin after flow alone (0 kPa on P-sel; n=3), and adhesion on casein after insonation at 122 kPa (122 kPa on Casein -i.e. control); n=3). Mean number of adherent microbubbles per 10 optical fields + standard deviation. Insonated capillaries exhibited significantly greater adhesion ($p<0.05$) than that of the flow only or insonated capillaries at each condition examined. The break in vertical scale may be noted.

FIG. 11 illustrates an epifluorescence microscopy observations (**FIGS**. **11(A), 11(B), 11(C)**) and ultrasound backscatter imaging (**FIGS. 8(D), 8(E), 8(F)**) of adherent microbubbles. Microcapillaries infused with buffer alone show no microbubble adhesion (**A**) and no ultrasound signal (dashed box illustrates microcapillary location) (**FIG**. **11 (D)**). Few adherent microbubbles are visible in flow-only microcapillaries (**FIG**. **11 (B)**), and the corresponding echo is identifiable but weak. A large number of adherent microbubbles are present in a microcapillary exposed to radiation force at 122 kPa (**FIG**. **11 (C)**), and the corresponding echo is strong. Scale bar represents 5 μm.

FIGS. 12(A)-(B) schematically illustrate various em-

bodiment (or partial embodiments thereof) of the present ultrasound catheter system.

FIG 13 provides a plan schematic view of the microfluidic flow-focusing device or in-situ device.

FIGS. 14(A)-(B) provide a schematic elevation view of embodiments of the catheter system having occlusion or sealing systems.

DETAILED DESCRIPTION

[0021] **FIG. 1** provides a schematic illustration of an embodiment (or partial embodiment) of the present invention ultrasound catheter system **102** for providing therapy to a treatment site at one or more locations of a subject. The system **102** may comprise a tubular member **118** such as a catheter or multiple catheters. The catheter(s) **118** having a proximal region **115** and distal region **117**, whereby said distal region 117 is adapted or configured to be advanced to or in proximity to the subject's treatment site. It should be appreciated that any one of the catheters as shown may be a plurality of catheters and any given catheter may have one or more lumens or channels therein. The system further comprises a microbubble reservoir **132** in hydraulic communication with the tubular member. The microbubble reservoir is **132** may be located in the proximal region **115** and/or the proximal region **117** as desired or required. The microbubble reservoir is **132** may be adapted to release microbubbles that are intended to be located into or proximal to the treatment site. The system further comprises an ultrasonic energy **112** source in communication with the proximal region **115** and/or distal region **117** of the tubular member **118.** The ultrasonic energy **112** may be capable of: imaging the treatment site, and/or rupturing the microbubbles. The ultrasonic energy **112** may be located outside or at least partially surrounding the subject **113** or patient. The system further comprises a control circuitry **100** or controller configured to send electrical activation to the ultrasonic energy source **112** or any components or subsystem affiliated with the catheter system **102.** Further, the ultrasonic energy source **112** may provide ultrasonic radiation forces for translating the microbubbles into or in the vicinity of the treatment site; or alternatively the mechanical forces may be provided for translating the microbubbles into or in the vicinity of the treatment site, as well as a combination of both mechanical and ultrasonic forces (acoustic wave) to achieve the desired or required result.

[0022] The tubular member **118** and other components and subsystems affiliated with the catheter system **102** may be manufactured in accordance with a variety of techniques known to an ordinarily skilled artisan. Suitable materials and dimensions can be readily selected based on the natural and anatomical dimension of the treatment or diagnosis site and on desired percutaneous access site or exterior.

[0023] For example, in an exemplary embodiment, the tubular body proximal region **115** and/or distal region **117** comprises a material that has sufficient flexibility, kink resistance, rigidity and structural support to push the ultrasound energy source 112 through the patient's vasculature or organ to a treatment site or vicinity thereof. Examples of such materials include, but are not limited to, extruded polytetrafluoroethylene ("PTFE"), polyethylenes ("PE"), Pebax - made by Arkema, polyamides and other similar materials. I n certain embodiments, the tubular body proximal region 115 and/or distal region **117** is reinforced by braiding, mesh or other constructions to provide increased kink resistance and ability to be pushed. For example, nickel titanium or stainless steel wires can be placed along or incorporated into the tubular member or body 118 to reduce kinking. For example, various guidewires, sheaths and additional tubular members may be implemented to handle the communications, navigations, controlling and imaging, etc.

[0024] It should be appreciated that the aforementioned catheter device, reservoir, ultrasound, and controller may be disposed entirely inside the applicable location of the subject as desired or required, outside the location of the subject as desired or required or a combination of inside or outside the location of the subject. The one or more locations of the subject may be an organ. The organ may include hollow organs, solid organs, parenchymal tissue, stromal tissue, and/or ducts. The one or more locations of the subject may be a tubular anatomical structure. The tubular anatomical structure may be a blood vessel. Further, for example, the treatment site may be a vasculature treatment site comprising at least one of the following: stenosis region or any region exhibiting vascular disease.

[0025] In an approach, a manifold and/or axis port **114** couples several therapeutic and/or diagnostic devices typified by device **116** to the catheter system **102.** A syringe, flow-driver or pumping device **124** is also in communication with the manifold **114.** The catheter system **102** in turn may be delivered through a guide sheath **120** that may be in communication with a navigation guide **122.** In operation the physician or user inserts one or more such catheter system **102** into the body of the subject **113**, for instance on going into the leg, chest or skull (or other anatomical part or parts or subject region or regions to cover the hollow or solid organs, blood vessels, etc.) under imaging guidance or other applicable examination or intervention. The same or similar ultrasound visualization may be used to follow the progress of the one or more implant(s) both acutely and chronically. This catheter device may have various interior and peripheral lumens, chambers and channels. Such interior and peripheral lumens, chambers and channels may be used to deliver other devices and perform various diagnostic functions. For example, each lumen, chamber, and channel may communicate with a separate port of the manifold 114. A lumen, chamber or channel may contain a pressure transducer 128. Other lumens and channels may be devoted to an optical or other type of cell counter device, for example, as shown generically as device 119 in

FIG. 1. Such a device may operate with two optical fibers (otpical device or counter) located in two separate lumens and/or ports to measure the number of and viability of cells, agents, drugs or microbubbles delivered by the catheter. An example of fiber optics related application/technology is discussed in U.S. Patent Application Serial No. 10/444,884, filed May 23, 2003 (U.S. Application No. 2003/0204171, published October 30, 2003).

[0026] An example of systems and methods that may be implemented with various embodiments of the present invention are provided in the following commonly owned Applications: U.S. Patent Application Serial No. 10/444,884, filed May 23, 2003 (US Application No. 2003/0204171, published October 30, 2003); PCT Application No. PCT/US2005/026738, filed July 28, 2005; and PCT Application No. 2006/005876, filed February 16, 2006.

[0027] It should be appreciated that as discussed herein, a subject may be a human or any animal. It should be appreciated that an animal may be a variety of any applicable type, including, but not limited thereto, mammal, veterinarian animal, livestock animal or pet type animal, etc. As an example, the animal may be
laboratory animal specifically selected to have certain characteristics similar to human (e.g. rat, dog, pig, monkey), etc. It should be appreciated that the subject may be any applicable human patient, for example.

[0028] **FIGS. 2(A)-(C)** schematically illustrate various embodiments (or partial embodiments) of the present invention ultrasound catheter system for providing therapy to a treatment site at one or more locations of a subject. The catheter system **202** may comprise a tubular member **218** such as a catheter or multiple catheters. The catheter(s) having a proximal region and distal region, whereby said distal region is adapted or configured to be advanced to or in proximity to the subject's treatment site. It should be appreciated that any one of the catheters **218** as shown may be a plurality of catheters and any given catheter may have one or more lumens therein. The system further comprises a microbubble reservoir **232** in hydraulic communication with the tubular member **218** and any lumens, channels, controllers or communication devices. The microbubble reservoir **232** is adapted to release microbubbles that are intended to be located into or proximal to the treatment site **210** at the desired or applicable location **211** of the subject. The system **202** further comprises an ultrasonic energy source **212** in communication with the distal region (or other region as desired or required) of the tubular member **218** (or other components or subsystems of the present invention). The ultrasonic energy is adapted for or capable of: imaging the treatment site **210**, and rupturing the microbubbles.

[0029] The system **202** further comprises a control circuitry **200** configured to send electrical activation to the ultrasonic energy source **212**, as well as other components and subsystems of the present invention. Further, the ultrasonic energy source **212** may provide ultrasonic radiation forces for translating the microbubbles into or in the vicinity of the treatment site **210** at the desired or applicable location **211** of the subject; or alternatively the mechanical forces may be provided for translating the microbubbles into or in the vicinity of the treatment site **210**, as well as a combination of both mechanical and ultrasonic forces (acoustic wave) to achieve the desired or required result. It should be appreciated that the aforementioned catheter **218**, reservoir **232**, ultrasound **212**, and controller **200** may be disposed entirely inside the applicable location of the subject, outside the location of the subject or a combination of inside or outside the location of the subject. The one or more locations **211** of the subject may be an organ. The organ may include hollow organs, solid organs, parenchymal tissue, stromal tissue, and/or ducts. The one or more locations **211** of the subject may be a tubular anatomical structure. The tubular anatomical structure may be a blood vessel. Further, for example, the treatment site **210** may be a vasculature treatment site comprising at least on of the following: stenosis region or any region exhibiting vascular disease. Further, for example, the treatment site **210** may be a vasculature treatment site and/or a diagnostic site.

Development of transducer / instrumentation to optimize delivery of a therapeutic agent by microbubble carrier.

[0030] Spatially localized, focused, non-invasive / minimally invasive treatments require appropriate non invasive real time imaging to guide the localization of the therapeutic (focal) region with respect to selected target site in the context of surrounding anatomy. This point may seem simple but it has profound implications for non-invasive treatment. This paradigm further suggests attention be paid to ensuring that the focused treatment zone be accurately and reliably aligned with whatever non-invasive imaging is used. The ideal model would be that the image plane is coincident with the therapeutic point, line or plane. Frequently, a small imaging array is placed centrally within an aperture "cut out" from a larger therapeutic array. Rosenschein [21] describes a 94 mm diameter therapeutic array into which a 7.5 MHz annular array is placed in concentric fashion. The system was used successfully for *in vitro* thrombolysis in bovine artery segments. Unger [22] describes (at least conceptually) a transducer design incorporating therapeutic and imaging array elements with a common front face plane. In this example, the therapeutic array is placed within a hole in the imaging array. A large central "hole" in an array aperture gives rise to a near-field blind spot and distorted sidelobe patterns - typically grating lobe related due to the poor spatial sampling implicit by virtue of the "hole" in the aperture. Until now, much work has involved fixturing an imaging array with respect to a therapeutic focused transducer / array [23-25]. An integrated imaging and therapeutic array, for example, was described by the University of Washington [26]. There is, however, no reason to believe that such an "integrated" array comprises

exactly coincident "therapeutic" and imaging arrays as proposed here. The precise need for defining a required level of "integration" is a function of the particular application.

[0031] In the context of microbubble imaging, Bouakaz [27] has described a dual frequency transducer (0.9 MHz and 2.8 MHz) array using interspersed elements. The element spacing is 0.5 mm - i.e. λ spacing at 2.8 MHz. When using an interspersed element design it becomes doubly problematic to achieve adequate spatial sampling. Further, only <50% of potential active area for each array (in isolation) is available. This loss of active area limits maximal acoustic power delivery. Forsberg [28] has also described a multifrequency array in which three linear arrays (2.5MHz, 5MHz and 1 OMHz) were placed side-by-side with a common focal range (50 mm). This approach works well within the one fixed focal region but lacks the versatility to address other ranges.

[0032] In an aspect of an embodiment of the present invention, there may be provided the imaging array immediately over the therapeutic array. Some advantages of an embodiment of the present invention configuration may be illustrated in **Fig3. FIGS. 3(A)-(C)** schematically illustrate the arrays of the Forsberg array **(see FIG. 3(A))** having elevational view - field intersection at one preselected range; Bouakaz array **(see FIG. 3(B))** with alternating elements of high and low frequency and having poor sampling and 50% area use per array; and an exemplary present invention embodiment of the stacked arrays **(see FIG. 3(C))** having fine sampling and 100% area usage. The transducer operating frequency may be inversely related to device thickness. The High and Low frequency transducer components denoted: HF and LF, respectively.

[0033] **FIG. 4** schematically illustrate an embodiment (or partial embodiment) of the present invention ultrasound catheter system **402** for providing therapy (as well as diagnostic if desired or required) to a treatment site at one or more locations of a subject. The catheter system **402** comprises a tubular member such as a catheter body **418** such or multiple catheters, needles, or lumens. The catheter(s) having a proximal region and distal region, whereby said distal region is adapted or configured to be advanced to or in proximity to the subject's treatment site such as a stenotic risk region **410.** It should be appreciated that any one of the catheters **418** as shown may be a plurality of catheters and any given catheter may have one or more lumens therein. The system further comprises a microbubble reservoir, port or channel **433** in hydraulic communication with the tubular member **418** and any lumens, channels, controllers or communication devices related to the catheter system. The microbubble reservoir, port or channel **433** is adapted to release microbubbles that are intended to be located into or proximal to the treatment site **410** at the desired or applicable location, such as a vessel or vessel wall **411** of the subject. The system **402** further comprises an ultrasonic energy source **412** in communication with the distal region (or other region as desired or required) of the tubular member **418** (as well as other components or subsystems of the present invention). The ultrasonic energy is adapted for, or capable of: imaging the treatment site **410**, (some embodiments, for example, optionally pushing bubbles using ultrasound radiation force [29]), and rupturing the microbubbles. For instance, therapeutic array **436** for bursting the microbubbles are provided (e.g., at low frequency LF or as desired or required). Further, an imaging array **437** for imaging (e.g., at high frequency array HF or as desired or required).

[0034] Still referring to **FIG. 4**, the system **402** further comprise (although not shown) a control circuitry configured to send electrical activation to the ultrasonic energy source, as well as other components and subsystems of the present invention. Further, the ultrasonic energy source may provide ultrasonic radiation forces for translating the microbubbles **434** into or in the vicinity of the treatment site **410** at the desired or applicable location **411** of the subject; or alternatively the mechanical forces may be provided for translating the microbubbles into or in the vicinity of the treatment site **410**, as well as a combination of both mechanical and ultrasonic forces (acoustic wave) to achieve the desired or required result.

[0035] It should be appreciated that the aforementioned catheter **418**, microbubble reservoir or channel **433**, ultrasound source(s) **412**, and controller may be disposed entirely inside the applicable location of the subject, outside the location of the subject or a combination of inside or outside the location of the subject. The one or more locations **411** of the subject may be an organ. The organ may include hollow organs, solid organs, parenchymal tissue, stromal tissue, and/or ducts. The one or more locations **411** of the subject may be a tubular anatomical structure. The tubular anatomical structure may be a blood vessel. Further, for example, the treatment site **410** may be a vasculature treatment site comprising at least on of the following: stenosis region or any region exhibiting vascular disease. Further, for example, the treatment site **410** may be a vasculature treatment site and/or a diagnostic site.

[0036] As such, the approach illustrated in **FIG. 4**, provides, for instance, a catheter for delivery of drug loaded bubbles, ultrasound imaging of bubbles / tissue, and ultrasound-based bubble destruction / drug delivery.

[0037] The imaging transducer/transducer array and the therapeutic transducer/transducer array may be identical. Whereas it is sometimes necessary to optimize two transducers for two functions it is also feasible, if the transducer possesses sufficient performance versatility (e.g. high frequency bandwidth and high power capability) to use the same transducer for both imaging and therapeutic function.

Ultrasound-triggered release of rapamycin from microbubbles attenuates SMC proliferation over 48 hrs *in vitro.*

[0038] As discussed above, the chemical and biologi-

cal properties of rapamycin and why it is the benchmark reagent for preventing SMC proliferation associated with vascular injury in vivo. This established the rationale for choosing rapamycin for ultrasound-triggered microbubble carrier release. Multiple groups have shown that treatment of cultured SMCs with rapamycin reduces SMC proliferation [12, 30]. However, delivering of rapamycin via ultrasound triggered release from a microbubble carrier has not been performed.

Exemplary Design/Experiment

[0039] Ultrasound was applied to rat smooth muscle cells in conjunction with modified ultrasound microbubbles containing rapamycin in their shells. The microbubbles were prepared by co-inventor *A. L. Klibanov* at UVA. Microbubbles were formed by self-assembly of a lipid monolayer during the ultrasonic dispersion of decafluorobutane gas in an aqueous micellar mixture of phosphatidylcholine (2mg/ml) and Polyethylene Glycol (PEG) stearate (2 mg/ml) with rapamycin (0.2 mg/ml) and/or a trace amount of a fluorescent dye DiI (Molecular Probes, Eugene, OR), similarly to the procedure described previously [31]. Fluorescently labeled DiI microbubbles were used as a control to ensure that the microbubble vehicle alone did not cause an effect on the cells. The rapamycin drug, dissolved in 100% ethanol, was also used as a control with which to compare the effect of the rapamycin microbubbles. We assured a strong adherence of cells to the OptiCell (Biocrystal, Westerville, OH) flasks by plating them with fibronectin for 24 hrs prior to plating any cells. Rat SMCs were plated at a low density and allowed to grow for 48 hrs in DF10 media inside each of 12 OptiCells. Digital phase microscopy light images of the cells were taken at 5 hrs prior before treatment to establish baseline conditions. All images were taken at 4X magnification. 24 hrs after plating, the media was replaced with fresh media containing either the DiI microbubbles (vehicle control), rapamycin drug (drug control), or rapamycin microbubbles. The microbubbles (DiI or rapamycin) were added to the OptiCells at a concentration of $10x10^6$ bubbles/ml and the rapamycin was added at a concentration of 10 ng/ml. The microbubble concentrations were chosen such that the number of microbubbles added contained an equivalent amount of rapamycin, ~10 ng/ml. We ensured that the drug had an effect even without prolonged exposure by taking half of the OptiCell flasks and giving them treatment for only two hours. After two hours the drug/bubble-containing media was replaced with fresh media. The cells in the OptiCell flasks received one of the following 6 treatments: DiI bubbles for 48 hours, rapamycin drug for 48 hours, rapamycin bubbles for 48 hours, DiI bubbles for 2 hours, rapamycin drug for 2 hours, rapamycin bubbles for 2 hours. All conditions were tested in duplicate.

[0040] Following the placement of fresh media and microbubbles into each OptiCell, ultrasound was applied to the entire area of cell growth. One at a time, each OptiCell was horizontally placed into a water bath (~37°C). A focused 1 MHz (Panametrics, Waltham, MA) transducer was immersed in the water and located directly above the cells. A motion controller was used to traverse the transducer across the aperture of the OptiCell so as to evenly apply ultrasound to the entire area of cell growth. A 1 MHz, 35% BW, Gaussian pulse was applied at a Pulse Repetition Frequency (PRF) of 1 kHz, 600 kPa peak, for the entire insonation time (9 mins.). Images were taken at 4 locations within each OptiCell. These locations were marked with a dot at the 5 hr time point. Subsequent images were taken at these same locations, 24 hours, and 48 hours after treatment. The OptiCells were stored in a 37°C incubator.

Results:

[0041] In **FIG. 5(A) and 5(B)**, we show that delivery of ~10 ng/ml of rapamycin by ultrasound-triggered release form a microbubble carrier prevented SMC proliferation, depicted as a change in cell number, compared to release of a fluorescent membrane dye, DiI (Invitrogen), from an equivalent number of microbubble carriers. Moreover, quantitative analysis in **FIG 5(D)**, shows that delivery of rapamycin (10 ng/ml) by ultrasound-triggered release from a microbubble carrier was not different from cells treated with free rapamycin drug (10 ng/ml) in the cell culture media. Similar results were observed in the set of 6 OptiCells which were only treated for 2 hours post ultrasound and then allowed to grow for 48 hrs (**FIG. 5(C) and 5(E)**). Thus, these results show (among other things) that rapamycin and an inert cell marking dye (DiI, FIG. 5(C)) can be delivered to SMCs by ultrasound-triggered microbubble carrier release.

[0042] Next, non-invasive ultrasound imaging can play a critical role in the guidance of the therapeutic ultrasound that will localize the release and transcellular membrane delivery of the rapamycin drug. For instance, **FIGS. 6** and **7** illustrate the current capabilities for fine-scale visualization of rodent vasculature. **FIG. 6** illustrates a bubble-specific image of vessel wall-bound molecular-targeted (anti-VCAM-1) bubbles in the mouse common carotid artery (CCA) assessed using 10 MHz bubble specific ultrasound imaging (e.g., Sequoia scanner or other commercial clinical ultrasound scanner). **FIG. 7(A)** is a VisualSonics VEVO 770 image of a rat carotid at 40 MHz demonstrating fine spatial resolution. **FIGS. 7(B)** and **7(C)** are B-Mode, and contrast specific, rat carotid images acquired at 12 MHz and 10 MHz, respectively (e.g., Sequoia scanner).

Transducer and Instrumentation

[0043] An exemplary transducer solution for dual function imaging therapeutics is one in which the transducer elements are sufficiently versatile that they can accomplish both tasks - high frequency (HF) imaging and low frequency (LF) bubble manipulation/ breaking. This en-

ables a design in which the imaging plane and therapeutic planes are coincident. Deficiencies in these previous designs suggest the need for a superior solution.

[0044] The solution to the dual function requirement of the transducer (HF, high resolution, low intensity imaging and LF, high power bubble fracture) is to form a transducer with two active layers: one on top of the other (for example as shown in **FIG. 3(C)** or **FIG. 4**). Each layer is resonant at a widely disparate frequency - the lower one at about 1 - 2 MHz and the upper one at approximately 12 MHz. Conventional design wisdom relating to stacked transducer layers would suggest that the two transducer layers would cause high undesirable interference between the resonances associated with each of the layers. Nevertheless, our experience suggests that a two layer transducer will work provided that the transducer layers are well matched between each other and to the backing material.

[0045] In an approach, a prototype dual layer single element transducer was designed using 1:3 PZT/epoxy composite transducer layers. The acoustic impedance of each layer is approximately 15 MRayl. The backing is a dense metal (tungsten) loaded epoxy with an acoustic impedance of approximately 9 MRayl. This transducer was fabricated to our design by Vermon, Tours, France. The single element device, 1 cm in diameter and with a focal depth of 5 cm, was constructed to test the viability of the proposed dual layer approach. **FIG. 8(A)** illustrates the pulse-echo responses of the LF layer. The LF result exhibits a desired smooth, short duration, waveform. The high frequency layer in the current prototype exhibits a reflection artifact that we attribute to reflections between the rear of the low frequency layer and the backing block (**FIG. 8(B)**). In **FIG. 8(C)**, we show that we can substantially correct this deficiency by using an inverse filter designed to force the response to be more Gaussian (in the frequency domain). Alternatively, we will redesign and optimize the dual layer transducer using better matched transducer layers to minimize / eliminate internal reflections. An early FEA result for a modified design, using a better matched backing (i.e. 15 MRayl), is shown in **FIG. 8(D).**

[0046] The transducer may be designed for any one of many clinical applications. It may be for transcutaneous use and comprise a conventional phased or linear array (flat or curved, or contoured anatomically or ergonomically as desired or required). It may also be designed for transesophagael, transvaginal, transuretha, transrectal or intra-operative use. Examples of each of these form factor transducers are known in the field - usually comprising similar transducer structures inside a plastic case adapted to the chosen anatomic use.

[0047] The transducer may also be formed in a catheter - as in intrasvascular ultrasound (IVUS). IVUS catheters are currently widely marketed in the US by Boston Scientific (Natick, MA) and Volcano (Rancho Cordova, CA). The Boston Scientific transducer typically comprises a single element that is rotated at high speed by a drive wire to form a coronal view. The transducer element in this transducer may be modified by changing its operating frequency (i.e. lowered to around 2-15 MHz) to make it suitable for breaking bubbles. The Volcano transducer is generally a circumferential phased array. Again, the frequency of the array design may be modified (i.e. lowered to around 2- aroound15 MHz) to make it suitable for breaking bubbles. It is possible to potentially use either a dual layer design -as described herein - or potentially use a modified design where a compromise between high frequency imaging and low frequency bubble breaking is selected - e.g., instead of attempting to operate imaging at about 25 MHz and breaking at about 2 MHz, a single wideband design at about 15 MHz is capable of about 8 MHz breaking and 20 MHz imaging. High bandwidth transducer design, such as by using multiple matching layers, for example, as known to those skilled in the art. As shown in **FIGS. 4** and **12**, for example, the catheter transducer may also include a continuous hollow port down which drug coated contrast is flushed during use. In this way, a stream of active contrast is emitted into the field of view of the transducer as shown schematically. (In clinical use, the blood flow in the coronaries is in the "right" direction - i.e. blood flow is moving in the distal orientation.).

[0048] Notice also that other formats of drug media delivery are possible. For example: free dissolved (e.g. alcohol) rapamycin (or other drug) may be transferred side by side with plain contrast microbubbles down the hollow port. As indicated in Price's 1998 Circulation paper ("Delivery of colloidal particles and red blood cells to tissue through microvessel ruptures created by targeted microbubble destruction with ultrasound" Vol. 98, No 13, pp1264-1267), local bubble breakage enables delivery of colloidal material (including potential drug in dissolved or undissolved form) across microcirculatory vessel walls. Bubble could be injected intravenously and dissolved rapamycin may be injected via the catheter port.

[0049] Normally lipid based bubbles are used. Other shell materials may be used - such as albumen-based or polymer-based shelled bubbles. Bubbles with these shell materials are known in the field.

Instrumentation

[0050] Among various options available, the SonixRP (Ultrasonix, Richmond, BC, Canada) is a versatile platform to use as the base instrumentation for implementing the invention. Of course, other scanner platforms may be procured or designed/built as is well known to those in the field. The RP, and its research capabilities (including high level software / hardware architecture), are described in detail in a recent publication [32] [32].

[0051] It should be appreciated a number of marketed technology systems and components may be implemented with the present invention such as by, but not limited to, the following: the medical ultrasound companies include: Philips, Siemens, General Electric - also Visual-

Sonics etc. However, it may be noted that these are not catheter based companies. BostonScientific and Volcano are the primary IVUS companies.

In vitro Radiation Force Enhanced Molecular Targeted Ultrasound

[0052] A problem encountered when using intravascular injected targeted contrast agent is that, except in very small vessels, only a very small fraction of the injected material will be sufficient close (<1μm) to have even a remote chance to form the intended molecular bond between ligand and receptor. *In vitro* studies of targeted microbubble adhesion on substrates of P-selectin have reported that only a small percentage of the perfused microbubbles were specifically retained under physiological flow conditions [e.g., Klibanov[33]]. Although detection of single microbubbles is possible [34], low efficiency of microbubble targeting requires a larger administered dose of microbubbles than would otherwise be required. Microbubbles exhibit rheological behavior similar to that of erythrocytes [35] and tend to migrate towards the center of the blood vessel. As most endothelial proteins extend only nanometers [36] from the endothelium, it is unlikely that many of the microbubbles flowing through the targeted vasculature come into contact with the intended molecular target. Microbubble attachment efficiency can be increased by moving circulating microbubbles into contact with the vessel wall, thus increasing the frequency of microbubble: target adhesive events. Dayton [37] and others [38] previously hypothesized that microbubble adhesion to the vascular endothelium may be enhanced by using ultrasound radiation forces to propel freely flowing microbubbles towards the vessel wall. Adhesion of microbubbles [39] and acoustically active liposomes [40] under applied acoustic pressure in an avidin: biotin model system has been examined, and adhesion of targeted microbubbles to cultured endothelial cells has been reported [39].

[0053] Acoustic radiation traveling through a continuous media produces a pressure gradient, which is experienced as a directional force by compressible bubbles in the acoustic field. Two components of this radiation force have been described: a primary force, which is directed away from the source, and a secondary force, which is typically attractive between ultrasound contrast microbubbles [41]. The behavior of single, free-stream microbubbles exposed to acoustic radiation has previously been examined rigorously [37, 41, 42]. Derivations of the magnitude of both primary and secondary forces in the linear range were presented by Dayton [37], assuming a low duty factor, a constant magnitude of pressure in each applied pulse, and a unidirectional pressure gradient. The primary radiation force is proportional to the negative time-averaged product of the microbubble volume and the spatial pressure gradient. For a microbubble driven at resonant frequency, assuming small-amplitude oscillations, the magnitude of the primary radiation force is defined by

$$F_1 = \frac{2\pi P_a^2 R}{\delta \omega_0 \rho c}\left[\frac{D}{T}\right] \quad (1)$$

where P_a is the peak applied acoustic pressure, R is the microbubble resting radius, δ is the total damping coefficient, ρ is the medium density, c is the velocity of sound in the bulk aqueous phase, and $\omega 0$ is the microbubble resonant frequency. This term is scaled by D/T for a pulsed field, where D is the pulse duration and 1/T is the pulse repetition frequency (PRF).

[0054] Targeting these microbubbles to P-selectin was achieved by conjugating the anti-P-selectin monoclonal antibody (mAb) Rb.40.34 [43] to the distal tips of PEG chains via a streptavidin link, as shown in **FIG. 9.** The preparation of the targeted microbubbles used in this experiment has been described in depth elsewhere [31, 44]. Trace amount (<1% of total lipid mass) of DiI lipid dye (Molecular Probes, Eugene, OR) was used as a fluorescence probe for epi-illumination microscopy. Microbubbles were conjugated to the targeting ligand the day of the experiment, and were stored on ice in C4F10-saturated Dulbecco's Phosphate Buffered Saline Solution (DPBS) (Invitrogen, Carlsbad, CA). Microbubble size distribution and concentration was determined with a Coulter counter (Beckman-Coulter, Miami, FL).

[0055] A 2.25 MHz, 0.5" diameter, 0.8" focal depth ultrasound transducer (Panametrics V306, Waltham, MA) was used in this study. At a Pulse Repetition Frequency (PRF) of 10 kHz, 40 sinusoidal cycles at a frequency of 2.0 MHz were applied. Microbubbles were insonated at acoustic pressures between 24.5 and 170 kPa. Upon cessation of insonation, 10 optical fields along a P-selectin coated microcapillary within the width of the applied ultrasound beam were observed and recorded. Alternatively, some flow chambers were exposed to 2 minutes of flow alone, without insonation, in order to assess microbubble binding in the absence of applied radiation force. The number of adherent microbubbles in each of 10 fields of view following insonation was determined offline. Microbubbles aggregates projecting normal to the optical plane (downward into the flow stream) were counted as a single bubble. Microbubble aggregation was assessed by counting the number of contiguous microbubbles adherent in the optical plane. Each flow chamber was used for a single experiment. Statistical significance was tested with a Student's t-test. We observed negligible binding of targeted microbubbles to casein-coated (i.e. control) microcapillaries both with and without the application of radiation force. We observed a statistically significant ($p<0.05$) increase in specific microbubble adhesion to P-selectin due to applied radiation forces at each of the microbubble concentrations examined. Applied radiation force increased targeted microbubble adhesion to P-selectin coated microcapillaries

16-fold at $75x10^6$ $B \cdot ml^{-1}$ and over 60-fold at $0.25x10^6$ $B \cdot ml^{-1}$ (or other sizes, volumes and ranges as required or desired).

[0056] Imaging of adherent microbubbles in flow chambers was also performed using 14 MHz ultrasound imaging (e.g., on a Siemens Sequoia or similar clinical scanner). Microbubbles were infused into the flow chamber as described above and exposed to 1 minute of flow alone at the indicated shear rate, followed by one minute of insonation at 122 kPa or 1 additional minute of flow only. It has also been determined that microbubbles attached to the target substrate by acoustic radiation force remain viable for ultrasound imaging. We observed no adherent microbubbles and received no ultrasound signal in microcapillaries infused with buffer alone (**FIG. 11(A), FIG. 11(D)**). A contrast signal is visible in **FIG.11(E)**, which shows an ultrasound image of a microcapillary infused with 2.5x106 B/ml for 2 minutes in the absence of acoustic pressure then flushed with buffer. A representative fluorescence microscopy field of view in this capillary is presented in **FIG. 11(C).FIG. 11(B). FIG. 11(C)** shows a representative optical field of view from a microcapillary infused with $2.5x10^6$ bubbles/ml exposed to 1 minute of flow only, 1 minute of insonation at 122 kPa and then saline flushed, in which extensive microbubble accumulation is evident. The corresponding echo shown in **FIG.11(F)** is very strong. This suggests that the microbubbles targeted by means of radiation force at an acoustic pressure of 122 kPa remain intact and echogenic.

[0057] In summary, we have demonstrated some of the key components of some of the embodiments of the present disclosure including, but not limited thereto, the following:

1. Rapamycin loaded microbubbles + ultrasound have a demonstrated, selective, anti-proliferative effect on rat SMCs.
2. VCAM-1, as well as other cell surface antigens including but not limited to PECAM, is upregulated in proliferating SMCs in the rat and other animal models of stenosis and human restenosis.
3. Fine resolution ultrasound imaging can visualize vasculature anatomy and achieve high sensitivity/high specificity bubble imaging.
4. Dual frequency transducers for: a) high frequency imaging, and b) low frequency radiation force / bubble fracture.
5. Radiation force can be used to improve bubble molecular VCAM-1 targeting attachment efficiency.

RELATED EXEMPLARY METHODS (AND RELATED SYSTEMS)

Single Element Transducer (typically non imaging capable).

[0058] Our preliminary data provided promising early results using a simple, axisymmetrically focused, single element transducer. What is required is a dual function (low frequency bubble "busting" plus high frequency imaging) transducer and associated instrumentation.

Transducer Array (typically imaging capable).

[0059] An exemplary design may comprise 1:3 composite piezoceramic - epoxy active layers stacked one over the other. (A "1:3" composite comprises piezoelectric ceramic posts embedded in a polymer matrix - i.e. the two components are electrically and mechanically in "parallel". The 1:3 configuration is the dominant composite configuration and is in widespread commercial use.). The composite material possesses approximate 50% ceramic volume fraction and possesses an acoustic impedance of approximately 15 MRayl. A dense, tungsten particle filled, backing block is used. A thin matching layer, approximately quarter wavelength matched for 12 MHz operation, is used over the top. A conventional filled silicone rubber lens will be used to obtain an elevation focus. The elevational focal depth is approximately 15 mm. Specifically, we use approximately 12 MHz B-Mode imaging resulting in <200 μm lateral resolution and axial resolution.. At this frequency, λ is 125 μm. Consequently, for practical f#'s, (i.e. 1-2) a 200 μm resolution is feasible. An array system provides more than sufficient scanning frame rate (> 100 frames/s for selected small fields of view - e.g.15 mm x 15mm). Focused ultrasound delivery is delivered at 1-2 MHz. We are able to control the region over which a therapeutic effect is obtained to approximately 3λ - i.e. approximately a 2 mm spot size.

High resolution, high sensitivity, high specificity, bubble imaging.

[0060] An objective is to provide anatomic B-Mode imaging capability, bubble specific imaging and application of bubble fracture pulses under user control. The anatomic B-Mode imaging are accomplished using standard B-Mode image formation techniques - i.e. optimized aperture apodization, fixed focus transmit, dynamic receive focusing, signal detection and scan conversion. Bubble specific imaging will be provided by using "Pulse Inversion"(PI)[45] - i.e. 1, -1 transmit polarity/amplitude; followed by "1"+"-1" processing to eliminate the linear component). If necessary other bubble specific techniques such as amplitude scaling (i.e. 1,2 transmit polarity/amplitude; followed by (2x"1") - "2" processing [46]) and the combination of PI and amplitude scaling (e.g. -1,2,-1 transmit polarity/amplitude; followed by "-1"+"2"+"-1" processing [47]).

Low frequency, bubble pushing and bubble destruction.

[0061] These modes use the low frequency elements of the array. The design of an embodiment for the trans-

ducer comprises less than a total of 128 elements (96, 12 MHz elements and 24, 2 MHz elements). In this way, by simply reprogramming the selected transducer apertures from the available 128 transducer connector channels, we can switch between imaging and therapeutic modes of operation.

Design rapamycin microbubble carrier system capable of ultrasound-triggered release

Bubble making and rapamycin incorporation.

[0062] Microbubbles are prepared by self-assembly of a lipid monolayer during the ultrasonic dispersion of decafluorobutane gas in the aqueous micellar mixture of phosphatidylcholine and PEG stearate (2 mg/ml) with rapamycin (0.2 mg/ml) and/or a trace amount of a fluorescent dye DiI (Molecular Probes, Eugene, OR), similarly to the procedure described earlier [48]. In some instances, membrane thickening is achieved by addition of glycerol trioleate (thicker microbubble shell will harbor increased amounts of rapamycin) [49]. Free lipid, dye and rapamycin, not incorporated in the bubble shell is removed by sequential (3x) centrifugal flotation (100xg, 5 min), with the recycling of the first wash to save reagents.

Rapamycin quantitation.

[0063] Robust and sensitive high performance liquid chromatography (HPLC) procedures are described in the literature for clinical assays. We have HPLC available in our laboratory and will implement such a procedure [50]. Briefly, the sample being tested (microbubbles or media) is lyophilized and redissolved in chlorobutanol, centrifuged to remove sediment; samples placed in the autosampler vials and HPLC performed with UV detection against a calibration curve with a known amount of rapamycin.

Rapamycin release by ultrasound: in vitro functional bubble destruction testing.

[0064] An aqueous saline dispersion of rapamycin-containing microbubbles (10^6-10^7/ml particle concentration) will be placed in an OptiCell (USA Scientific, Ocala, FL) in 10ml volume. We will destroy bubbles by ultrasound in the conditions described for the cell culture study, remove the microbubble particles from OptiCell and subject them to centrifugal flotation to prove that residual microbubbles (if present) will be removed from the samples. We will then perform rapamycin quantitation in the bubble-free infranatant by HPLC technique as described above.

Attachment of anti-VCAM-1 antibody to microbubbles.

[0065] Coupling of anti-VCAM-1 antibody to microbubble surface is performed by streptavidin coupling technique as described [44]. Briefly, during the preparation of microbubbles, 2 mol% of biotin-PEG3400-phosphatidylethanolamine is added to the lipid mixture. A streptavidin bridge technique is applied for biotinylated anti-VCAM-1 antibody coupling to the microbubble surface as described earlier for other antibodies [33, 51]. Biotinylation of antibody molecule is performed with biotin N-hydroxysuccinimide ester reagent at pH 7.5 in DPBS buffer. The degree of antibody biotinylation is tested using the HABA assay as described previously [e.g., Klibanov [33]]. By the adjustment of the antibody-to-biotin-NHS, an incubation ratio coupling of ~1 biotin per antibody will be achieved. The ELISA test on VCAM-1 antigen is used to confirm that biotinylation does not inactivate the antibody. Streptavidin-bubbles (10^9/ml) are incubated with biotinylated antibody on ice for 30 min; free antibody are removed from the bubbles by triple centrifugal flotation wash with degassed DPBS buffer in a bucket-rotor centrifuge (lOOxg, 5 min). After repeated flotations, the mean size of antibody-coated bubbles is normally -2.5 um, with >99% of the particles less than 8 um (particle size and concentration are evaluated with a Coulter Multisizer He instrument (Beckman Coulter, Miami, FL). The amount of attached antibody per bubble is tested by fluorescence spectroscopy labeling as described earlier; typically, ~10<5> antibody molecules per microbubble are attached by this technique [51].

[0066] **FIG.12(A)** schematically illustrate an embodiments (or partial embodiment) of the present ultrasound catheter system **1202** for providing therapy (as well as diagnostic if desired or required) to a treatment site at one or more locations of a subject. The catheter system **1202** may comprise a tubular member **1218** or other conduit or chamber, such or multiple catheters, needles, or lumens. The catheter(s) having a proximal region and distal region, whereby said distal region is adapted or configured to be advanced to or in proximity to the subject's treatment site or region **1210.** It should be appreciated that any one of the tubular member **1218** as shown may be a plurality of tubular or conduit members and any given catheter or the like may have one or more lumens therein. The system further comprises a microbubble reservoir **1232** in hydraulic communication with the port or channel **1233** and in hydraulic communication with the tubular member **1218** and any lumens, channels, controllers or communication devices related to the catheter system. The microbubble reservoir **1232** and port or channel **1233** is adapted to release microbubbles that are intended to be located into or proximal to the treatment site **1210** at the desired or applicable location **1211** of the subject **1211**, such a vessel, organ, anatomical structure, anatomical tubular structure, or duct, etc.. The system **1202** further comprises an ultrasonic energy source(s) **1212** in communication with the distal region (or other region as desired or required) of the tubular member **1218** (as well as other components or subsystems or components of the present disclosure). The ultrasonic energy is adapted for or capable of: imaging the

treatment site **1210,** and rupturing the microbubbles. For instance, therapeutic array **1236** (comprising a predetermined ultrasound system design as desired or required) for bursting the microbubbles are provided (e.g., at low frequency LF or as desired or required). Further, an imaging array **1237** (comprising a predetermined ultrasound system design as desired or required) is provided for imaging (e.g., at high frequency array HF or as desired or required). Further yet, the ultrasonic energy source **1238** (comprising a predetermined ultrasound system design as desired or required) may provide ultrasonic radiation forces for translating or transporting the microbubbles **1234** (e.g., at low frequency LF or high frequency HF, or combination thereof, or as desired or required) into or in the vicinity of the treatment site **1210** or region at the desired or applicable location **1211** of the subject.

[0067] Still referring to **FIG. 12(A)**, the system **1202** further comprise (although not shown) a control circuitry configured to send electrical activation to the ultrasonic energy source, as well as other components and subsystems of the present disclosure. Further, regarding the translation or transportation of the microbubbles or applicable medium, mechanical forces may be provided may be provided in place of the ultrasound forces (acoustic wave) or in combination with the ultrasound for translating the microbubbles into or in the vicinity of the treatment site **1210** to achieve the desired or required result.

[0068] It should be appreciated that the aforementioned catheter **1218**, microbubble reservoir **1232**, microbubble port or channel **1233**, ultrasound source(s) **1212**, and controller may be disposed entirely inside the applicable location of the subject **1211**, outside the location of the subject or a combination of inside or outside the location of the subject. The one or more locations **1211** of the subject may be an organ. The organ may include hollow organs, solid organs, parenchymal tissue, stromal tissue, and/or ducts. The one or more locations **1211** of the subject may be a tubular anatomical structure. The tubular anatomical structure may be a blood vessel. Further, for example, the treatment site **1210** may be a vasculature treatment site comprising at least on of the following: stenosis region or any region exhibiting vascular disease. Further, for example, the treatment site **1210** may be a vasculature treatment site and/or a diagnostic site.

[0069] **FIG.12(B)** schematically illustrate an embodiments (or partial embodiment) of the present ultrasound catheter system **1202** for providing therapy (as well as diagnostic if desired or required) to a treatment site at one or more locations of a subject. The catheter system **1202** may comprise a tubular member such as a catheter body **1218** such or multiple catheters, needles, conduits, housings, or lumens. The catheter(s) having a proximal region and distal region, whereby said distal region is adapted or configured to be advanced to or in proximity to the subject's treatment site or region **1210.** It should be appreciated that any one of the catheters **1218** as shown may be a plurality of catheters and any given catheter may have one or more lumens therein. The system further comprises a microbubble reservoir **1232** in hydraulic communication with the port or channel **1233** and in hydraulic communication with the tubular member **1218** and any lumens, channels, controllers or communication devices related to the catheter system. The microbubble reservoir **1232** may be single use microbubble dose and high concentration. Moreover, the reservoir **1232** may comprise multiple uses and have a variety of concentrations as desired or required. The microbubble reservoir **1232** and/or port or channel may be a capillary size or larger, or the microscale or smaller such as a microchip, lab-on-a-chip, or in-situ design. The microbubble reservoir **1232** and port or channel **1233** is adapted to release microbubbles that are intended to be located into or proximal to the treatment site **1210** at the desired or applicable location, such as a vessel or vessel wall **1211** of the subject. The system **1202** further comprises an ultrasonic energy source **1212** in communication with the distal region (or other region as desired or required) of the tubular member **1218** (as well as other components or subsystems of the present disclosure). The ultrasonic energy is adapted for or capable of: imaging the treatment site **1210**, and rupturing the microbubbles. For instance, therapeutic array **1236** for bursting the microbubbles are provided (e.g., at low frequency LF or as desired or required). The therapeutic array **1236** comprises a bubble rupture transducer that may be a rotating type; or may be a non-rotating type and be aligned with the radiation force transducer **1238** (or any combination thereof). Further, an imaging array **1237** is provided for imaging (e.g., at high frequency array HF or as desired or required). The imaging array **1237** may be rotating or non- rotating and may be a single element or multiple element (or any combination thereof). Further yet, the ultrasonic energy source **1238** may provide ultrasonic radiation forces for translating or transporting the microbubbles **1234** (e.g., at low frequency LF or high frequency HF, or combination thereof, or as desired or required) into or in the vicinity of the treatment site **1210** at the desired or applicable location **1211** of the subject. The radiation force transducer **1238** may be elongated and non- rotating. Alternatively, the shape may also vary and it may rotate as well. Alternatively, rather than a radiation force transducer, a means for transporting or translating may be implemented, such as mechanically or electrically. For instance, but not limited thereto, ejecting the bubbles with sufficient peripheral oriented velocity so as to translate quickly to the vessel wall.

[0070] Still referring to **FIGS. 12(A)-(B)**, the system **1202** further comprise (although not shown) a control circuitry configured to send electrical activation to the ultrasonic energy source, as well as other components and subsystems. Further, regarding the translation or transportation of the microbubbles or applicable medium, mechanical forces may be provided in place of the ultrasound forces (acoustic wave) or in combination with the ultrasound for translating the microbubbles into or in the

vicinity of the treatment site **1210** to achieve the desired or required result.

[0071] It should be appreciated that the aforementioned catheter **1218**, microbubble reservoir **1232**, microbubble port or channel **1233**, ultrasound source(s) **1212**, and controller may be disposed entirely inside the applicable location of the subject, outside the location of the subject or a combination of inside or outside the location of the subject. The one or more locations **1211** of the subject may be an organ. The organ may include hollow organs, solid organs, parenchymal tissue, stromal tissue, and/or ducts. The one or more locations **1211** of the subject may be a tubular anatomical structure. The tubular anatomical structure may be a blood vessel. Further, for example, the treatment site **1210** may be a vasculature treatment site comprising at least on of the following: stenosis region or any region exhibiting vascular disease. Further, for example, the treatment site **1210** may be a vasculature treatment site and/or a diagnostic site.

[0072] Still referring to **FIGS. 12(A)-(B)**, for example (as well as other embodiments discussed herein), the system **1202** may comprise, but not limited to the following:

- Imaging transducer may be scanned single element or array;
- Orientation of scanning transducer/array may be annular format per conventional;
- IVUS or may be longitudinal (or other) format;
- Longitudinal format is like shown here for the radiation force transducer and may be similar to the Siemens AcuNav intracardiac catheter transducer array;
- Radiation force transducer may be a single element, focused element;
- It might be an annular array for multiple focal option;
- Frequency of each transducer/array may be different;
- Radiation force transducer may be high frequency;
- Imaging radiation may be high frequency;
- Rupture radiation may be low frequency;
- Rupture and imaging could be coincident - one over the other;
- Bubbles are conceptually injected via a port;
- Bubbles may be injected freely via the same access catheter (i.e. ~2mm tube or as desired);
- Bubbles may be saved in a single use highly concentrated from near the catheter tip. This would allow us to use a smaller number of bubbles. Keeping the bubbles in high concentration (i.e. low rate of outward diffusion) allows them to be time stable);
- Bubbles may be monodisperse (all same size), but not necessarily;
- In principle, bubble dispersions can be sorted.

[0073] **FIG. 13** illustrates a schematic plan view of the "On-chip generation of microbubbles as a practical technology for manufacturing contrast agents for ultrasonic imaging" by Kanaka Hettiarachchi, Esra Talu, Marjorie L. Longo, Paul A. Dayton and Abraham P. Lee Lab on a Chip, 2007, 7, 463-468. Provided is the soft molded PDMS (silicone) based micro flow chamber below. An embodiment of the present disclosure provides a segment of a device that easily fits at the tip of a catheter. This approach has many features and characteristics:

1. Increased versatility -can vary shell composition (i.e. potentially drug/gene payload and concentration "on the fly");
2. Enables otherwise unfeasible bubbles. Making the bubbles at the tip means that stability problems are mitigated. The bubbles only have to survive a few seconds before therapeutic delivery. This may enable less stable chemical formulations or less stable bubble (i.e. shell/gas) permutations. Currently, gas is limited to one with very low rate of diffusion (i.e. high molecular weight). The new design enables the use of new gases or light gases at a minimum. This area isn't properly explored yet in our opinion.
3. Existing problems with bubble stability that require complex handling are circumvented.

[0074] Still referring **FIG. 13, FIG 13** provides a schematic plan view of the microfluidic flow-focusing device or in-situ device. The microfiuid device may be less than about 1 mm and therefore can be fit inside a catheter for example. The arrows indicate direction of flow of liquid inlet(s) and gas inlet.

[0075] It should be appreciated that the widths and heights may be larger or smaller as required. The contours and shapes may vary as well.

[0076] **FIG. 14(A)** provides a schematic elevational view of an embodiment (or patial embodiment) or approach of the present disclosure that provides a single occlusion balloon to temporally stop flow - distal to transducer and drug bubble port. The balloon may be released (or partially released) after procedure (or during the procedure) and drug bubble residual or other medium flows systemically or as available.

[0077] **FIG. 14(B)** provides an embodiment similar to device as shown in **FIG. 14(A)**, however the instant embodiment or approach of the present disclosure provides a dual occlusion balloon to stop flow (or hinder flow) and create a sealed vessel section (or partially sealed section) in which drug (or applicable medium) is injected, delivered and then flushed to eliminate systemic delivery concerns. The instant approach may also include second port well separated from first so as to permit flush in from one and vacuum out at other - i.e. ports upstream and downstream and close to each of the balloons (or located as desired or required).

[0078] The balloons may be any available sealing, occluding or blocking designs, structure, or devices available to those skilled in the art (or so as to provide partial occlusion when applicable or desired).

[0079] Examples of balloon (or occlusion) related cath-

eter devices and associated methods are provided below.

1. U.S. Patent No. 6,626,861, September 30, 2003, "Balloon catheter apparatus and method", Hart, et al.
2. U.S. Patent Application Publication No. 2006/0235501, October 19, 2006, "Stent supplying device", Igaki, et al.
3. U.S. Patent Application Publication No. 2007/0055132, March 8, 2007, "Catheter device," Camus, et al.
4. U.S. Patent No. 5,868,708, February 9, 1999, "Balloon catheter apparatus and method", Hart, et al.
5. U.S. Patent Application Publication No. 2006/0189928, August 24, 2006, "Catheter device", Camus, et al.
6. U.S. Patent Application Publication No. 2008/0243233, October 2, 2008, "Device and Methods for Treatment of Vascular Bifurcations", Ben-Muvhar, et al.
7. U.S. Patent No. 5,222,970, June 29, 1993, "Method of and system for mounting a vascular occlusion balloon on a delivery catheter", Reeves, et al.
8. U.S. Patent No. 5,707,354, January 13, 1998, "Compliant catheter lumen and methods", Salmon, et al.
9. U.S. Patent Application Publication No. 2003/0163192, August 28, 2003, "Methods for vascular reconstruction of diseased arteries", Wallace, et al.
10. U.S. Patent Application Publication No. 2002/0169496, November 14, 2002, "Methods for vascular reconstruction of diseased arteries", Wallace, et al.
11. U.S. Patent Application Publication No. 2008/0103443, May 1, 2008, "Balloon catheter for treating hardened lesions", Kabrick, et al.
12. U.S. Patent No. 6,565,601, May 20, 2003, "Methods for vascular reconstruction of diseased arterie, Wallace, et al.
13. U.S. Patent No. 5,827,171, October 27, 1998, 'Intravascular circulatory assist device", Dobak, et al.
14. U.S. Patent No. 7,011,677, March 14, 2006, "Methods for vascular reconstruction of diseased arteries", Wallace, et al.
15. U.S. Patent No. 5,941,870, August 24, 1999, "Catheter system having a balloon angioplasty device disposed over a work element lumen", Jang, et al.
16. U.S. Patent Application Publication No. 2004/0158308, August 12, 2004, "Delivery catheter for ribbon-type prosthesis and methods of use", Hogendijk, et al.
17. U.S. Patent Application Publication No. 2006/0161103, "Catheter systems and methods for their use in the treatment of calcified vascular occlusions", Constantz, et al.
18. U.S. Patent Application Publication No. 2003/0199820, October 23, 2003, "Catheter systems and methods for their use in the treatment of calcified vascular occlusions", Constantz, et al.
19. U.S. Patent Application Publication No. 2002/0044907, April 18, 2002, "Catheter systems and methods for their use in the treatment of calcified vascular occlusions", Constantz, et al.
20. U.S. Patent Application Publication No. 2007/0049867, "System for treating chronic total occlusion caused by lower extremity arterial disease", Shindelman, et al.
21. U.S. Patent No. 5,041,089, August 20, 1991, "Vascular dilation catheter construction", Mueller, et al.
22. U.S. Patent No. 5,755,707, May 26, 1998, "Vascular dilating catheter", Miyagawa, et al.
23. U.S. Patent Application Publication No. 2004/0111145, June 10, 2004, "Vascular prosthesis for the treatment of abdominal aortic aneurysms, using a combined laparoscopic/ open and endovascular technique, and delivery system for releasing a prosthesis fitted with anchoring stents", Serino, et al.
24. U.S. Patent Application Publication No. 2007/0043389, February 22, 2007, "System for treating chronic total occlusion caused by lower extremity arterial disease", Shindelman, et al.
25. U.S. Patent Application No. 2003/0220666, November 27, 2003, "Solid embolic material with variable expansion", et al.
26. U.S. Patent No. 5,117,831, June 2, 1992, "Vascular catheter having tandem imaging and dilatation components", Jang, et al.
27. U.S. Patent No. 6.527.979, March 4, 2003, "Catheter systems and methods for their use in the treatment of calcified vascular occlusions", Constantz, et al.
28. U.S. Patent No. 5,447,503, September 5, 1995, "Guiding catheter tip having a tapered tip with an expandable lumen", Miller, et al.
29. U.S. Patent No. 7,198,637, April 3, 2007, "Method and system for stent retention using an adhesive", Deshmukh, et al.
30. U.S. Patent No. 5,415,634, May 16, 1995, "Catheter having helical inflation lumen", Glynn, et al.

Characteristics and features that may be implemented in whole or in part (in any permutation) with the various embodiments or partial embodiments as discussed throughout this document

[0080] An embodiment or approach of the present disclosure provides Dual use IVUS provides imaging plus therapy.

[0081] An embodiment or approach of the present disclosure provides Rapamycin bubbles (and other drugs with therapeutic effect - primarily antiproliferative but could be others - including dual drug use - such as one drug to precondition tissue for a second drug to operate

with efficacy).

Gene bubbles

[0082] An embodiment or approach of the present disclosure provides the use of cell-specific promoter constructs to target gene expression specifically to one or multiple cell types in combination or independently. This includes but is not limited to endothelial cell specific promoters (e.g. Tie-2, eNos), smooth muscle cell specific promoters (e.g. SMMHC, SM alpha-actin, SM22-alpha, myocardin), macrophages (e.g. mac-1) and promoter of these genesthat have been modified by mutating specific cis DNA sequences so as to limit inhibition of the promoter and increase activity. An example would be, but not limited, to a G/C mutation in the SM22a promoter which renders the promoter active in all smooth muscle cell phenotypes [e.g., Wamhoff et al, Circ Res, 2004]. Genes under control of a tissue selective promoter include but are not limited to anti-proliferative genes such p21, p53, KLF4 and proliferative genes such as PCNA. In one scenario, a proliferative gene is targeted to endothelial cell to promote re-endothelialization and an anti-proliferative gene is targeted to smooth muscle to prevent restenosis.

[0083] An embodiment or approach of the present disclosure provides molecular targeted bubbles (VCAM-1, PECAM, etc.). The targeting can be in context of diagnosis or therapeutic use of bubbles - or both. The targeting to be any disease with molecular marker on endothelial surface. For example, VCAM-1 for atherosclerotic plaque - including "vulnerable plaque" or $\alpha\varpi\beta_3$ for angiogenesis associated with cancer.

[0084] An embodiment or approach of the present disclosure provides radiation force and bubbles (which usually involves long pulse bursts, but not necessarily).

[0085] An embodiment or approach of the present disclosure provides IVUS catheter with drug bubble delivery port upstream.

[0086] An embodiment or approach of the present disclosure provides drug delivery "port" is plural and forms an annulus.

[0087] An embodiment or approach of the present disclosure provides a mechanically scanned single element transducer - mechanically scanning achieves the regional coverage.

[0088] An embodiment or approach of the present disclosure provides phased array transducer - side fire / annular fire. The phased array may be used for imaging and therapy.

[0089] An embodiment or approach of the present disclosure provides a combination transducer elements - high power/low frequency, low power high frequency.

[0090] An embodiment or approach of the present disclosure provides different transducer elements in different formats - e.g. phased array imaging plus scanned single element therapeutic.

[0091] An embodiment or approach of the present disclosure provides a single occlusion balloon to temporally stop flow - distal to transducer and drug bubble port (for instance, release balloon after procedure and drug bubble residual flows systemically).

[0092] An embodiment or approach of the present disclosure provides a dual occlusion balloon to stop flow and create a sealed vessel section in which drug is injected, delivered and then flushed to eliminate systemic delivery concerns (requires second port well separated from first so as to permit flush in from one and vacuum out at other - i.e. ports upstream and downstream and close to each of the balloons)

[0093] An embodiment or approach of the present disclosure provides a 3D scanning to record extent of problem lesion followed by automated 3D sweep across the lesion to achieve therapeutic effect - i.e. it may be time / procedure efficient for the physician to outline the 3D extent of the plaque and then have the system sweep the region by way of automated sequence of 1D lines to fully encompass the 2D surface of the 3D lesion. The "Track back" method, well known in IVUS, can be used "TrakBackII" from Volcano Corp for their array IVUS.

[0094] An embodiment or approach of the present disclosure provides a vulnerable plaque application as mentioned immediately above, except application is diagnosis of vulnerable plaque. (Further, it doesn't actually doesn't have to be 3D - but 3D is typically best). The means of differentiating vulnerable plaque comprises- any permutation of:

a. Using appropriate molecular targeted microbubbles (VCAM-1 for example).

b. Using microbubbles to detect microvasculature of vasa vasorum - an indicator of active vulnerable plaque (see for example, see reference Dutch group - Goertz, van der Steen et al. http://publishing.eur.nl/ir/repub/asset/7950/060908_Friilink,%20Martijn%20Egbert.pdf, Harmonic Intravascular Ultrasound Thesis, Martijn Frijlink, 2006 Delft, Netherlands).

c. Performing signal processing (attenuation/frequency vs. depth as per "virtual histology" of Volcano (Vince et al.)

d. Performing an elasticity based measurement to detect unusual softness of plaque (e.g., per known methods of transducer inside balloon described by M O'Donnell or measuring tissue response to pulsatile blood forces - Van Der Steen)

e. "Tissue thermal strain imaging": Identification of vulnerable atherosclerotic plaque using IVUS-based thermal strain imaging: Yan Shi; Witte, R.S.; O'Donnell,M.; Ultrasonics, Ferroelectrics and Frequency Control, IEEE Transactions in Volume 52, Issue 5, May 2005 Page(s):844 - 850 An embodiment or approach of the present disclosure sets forth to stabilize the vulnerable plague by delivery compounds such as basic FGF which promoter smooth muscle prolif-

eration and migration to stabilize the weak fibrous cap. We will refer to all analogous therapy approaches for treating brain aneurysms with cerebral microcoils. Micro-coils are delivered to the blood vessel wall where an aneurysm occurred to provide support for smooth muscle to proliferate and migrate and heal the aneurysm. An approach or embodiment promote, in the case, smooth muscle proliferation and migration, not inhibit it.

[0095] An embodiment or approach of the present disclosure provides a transducer(s) that may include any permutation of the following:

a. Single element capable of any or all of: radiation force, imaging, bubble rupture.
b. Phased array (in any format: longitudinal or annular) capable of any or all of: radiation force, imaging, bubble rupture.
c. Either or above wherein element(s) are dual (or triple) layer arranged to provide (typically) high power at lower frequency and lower power/fine resolution using high frequency.
d. Wherein the different transducers performing different functions are not arranged one over the other. Place an elongated radiation force transducer (or array) upstream of imaging/delivery zone (see figure). Then have an imaging transducer - imaging the bubbles that have been pushed to the zone of interest. Then have a delivery transducer. (Subsets also possible - such as dedicated elongated radiation force transducer plus combined imaging/delivery transducer (or array).
e. An embodiment or approach of the present disclosure provides a transducer(s) that can be formed from piezoelectric material (preferably ceramic but could be piezoelectric polymer PVDF). Alternatively transducers can be electrostatic, silicon (or other material) "MEMS" devices.

[0096] An embodiment or approach of the present disclosure provides a method for localized delivery of drug from drug loaded microbubbles using high intensity ultrasound wherein the location of the focal delivery is guided by an integral, real-time, coincident, ultrasound imaging system.

[0097] An embodiment (or partial embodiment) or approach of the present disclosure provides a method for localized drug delivery wherein the drug coated bubbles possess a selected molecular attachment ligand - such as VCAM-1, P-Selectin, etc. under realtime ultrasound image guidance, such as:

- dual targeting method - fast catch / slow hold
- variant on bubbles such as liposomes
- nanoparticle + bubble
- dual modality contrast Ultrasound + MRI contrast Bubble + ferrous
- potential of drug not being integrated in bubble shell but existing in free solution aside the bubbles and relying on bubble related sonoporation to result in preferential drug uptake.

[0098] An embodiment or approach of the present disclosure provides a drug that is rapamycin (antiproliferative, immunosuppressive, or antiinflammatory drug, such as rapamycin, tacrolimus, paclitaxel, dexamethasone, or an active analog or derivative, or combinations thereof.). The drug may be selected from a group comprising actinomycin-D, batimistat, c-myc antisense, dexamethasone, paclitaxel, taxanes, sirolimus, tacrolimus and everolimus, unfractionated heparin, low-molecular weight heparin, enoxaprin, bivalirudin, tyrosine kinase inhibitors, Gleevec, wortmannin, PDGF inhibitors, AG1295, rho kinase inhibitors, Y27632, calcium channel blockers, TRAM-34, IKCa channel blockers, amlodipine, nifedipine, and ACE inhibitors, S1P1 and/or S1P3 receptor antagonists, sphingosine kinase 1 inhibitors, synthetic polysaccharides, ticlopinin, dipyridamole, clopidogrel, fondaparinux, streptokinase, urokinase, r-urokinase, r-prourokinase, rt-PA, APSAC, TNK-rt-PA, reteplase, alteplase, monteplase, lanoplase, pamiteplase, staphylokinase, abciximab, tirofiban, orbofiban, xemilofiban, sibrafiban, roxifiban,, an anti-restenosis agent, an antithrombogenic agent, an antibiotic, an anti-platelet agent, an anti-clotting agent, an anti-inflammatory agent, an anti-neoplastic agent, a chelating agent, penicillamine, triethylene tetramine dihydrochloride, EDTA, DMSA (succimer), deferoxamine mesylate, a radiocontrast agent, a radio-isotope, a prodrug, antibody fragments, antibodies, gene therapy agents, viral vectors and plasmid DNA vectors.

[0099] An embodiment or approach of the present disclosure provides a subset of relevant bubble properties - dimensions, core gas, shell materials, etc. and including oily shell - decafluorobutane

[0100] An embodiment or approach of the present disclosure provides an acoustic radiation force that may be used to translate bubbles towards a selected vessel wall.

[0101] An embodiment or approach of the present disclosure provides microbubbles are targeted to blood vessels that routinely undergo and angioplasty and/or stenting (including balloon expansion stents and self-expanding stents), including but not limited to the coronary arteries, coronary artery branch points, carotid arteries, cerebral arteries, femoral arteries.

[0102] An embodiment or approach of the present disclosure provides a systemic injection of bubbles.

[0103] An embodiment or approach of the present disclosure provides a localized injection of bubbles - from catheter tip -preferably same catheter as imaging but potentially from separate one. See catheter cross-sectional drawing above.

[0104] An embodiment or approach of the present disclosure provides an ultrasound image guidance of bubbles in a highly bubble-specific mode using one of pulse

inversion, amplitude scaling ("power modulation") or combination of two ("contrast pulse sequences").

[0105] An embodiment or approach of the present disclosure provides an ultrasound intensity has therapeutic (drug delivery) effect, wherein ultrasound has cell death effect.

[0106] An embodiment or approach of the present disclosure provides the uses of a ultrasound catheter - about 1- about 2 MHz therapeutic, about 30 MHz imaging.

[0107] An embodiment or approach of the present disclosure provides a co-located transducer - imaging device overlaying the therapeutic device, imaging device residing in an aperture formed within center of therapeutic device (less desirable than overlaying).

[0108] An embodiment or approach of the present disclosure provides a synchronized operation - the imaging system is "gated" to never operating during the time of therapeutic operation.

[0109] An embodiment or approach of the present disclosure provides a therapeutic system "listens" for imaging system operation and inserts therapeutic pulses between imaging operations.

[0110] An embodiment or approach of the present disclosure provides an imaging system "listens" for therapeutic system operation and inserts imaging pulses between therapeutic operations.

[0111] An embodiment or approach of the present disclosure provides a "Pulse sequence" claims - X seconds (s) of therapeutic, followed by Y s of imaging, and so on for Z minutes.

[0112] An embodiment or approach of the present disclosure provides an integrating of this device on a catheter with other preferred catheter device options - e.g. balloon, pressure measurement, temperature measurement, blood sampling.

[0113] An embodiment or approach of the present disclosure provides a catheter with "over the wire" capability - the standard - has capability to be "threaded" over an in-place metal wire.

[0114] An embodiment or approach of the present disclosure provides a catheter that may be a derivative of the "Volcano" IVUS catheter (phased annular array). A therapeutic transducer - side firing - is placed near to the imaging annular array.

[0115] An embodiment or approach of the present disclosure provides a catheter that may be related to some extent to the "Boston-Scientific" IVUS catheter (mechanically scanned single element) i.e. the existing high frequency transducer element is replaced with a stack of low frequency (therapeutic) 1MHz element with 30 MHz imaging overlaid. Alternatively, there are two transducers side by side in close proximity.

[0116] An embodiment or approach of the present disclosure provides a catheter possessing an imaging transducer / array in any one or more of the following formats: single element transducer rotated in circumferential fashion to form coronal plane, circumferential array forming coronal plane, side-fire array and wherein the therapeutic array is in any one of more of the following formats: single element transducer rotated in circumferential fashion to form coronal plane, circumferential array forming coronal plane, side-fire array

[0117] An embodiment or approach of the present disclosure provides an imaging transducer / array is in any one or more of the following formats: single element transducer rotated in annular fashion to form coronal plane, annular array forming coronal plane, side-fire array and wherein the therapeutic transducer is single focused element or annular array.

[0118] An embodiment or approach of the present disclosure provides a pro-proliferative for filling up an aneurysm, occlusive treatment upstream of an angiogenic region associated with evolving cancer; Image guidance other than ultrasound; or other mechanisms for therapeutic delivery - such as heat as opposed to acoustic disruption.

[0119] Wherein the image guidance (other than ultrasound) includes one or more of: 1) X-ray and its derivatives (plain X-ray, realtime fluoroscopy and computed tomography [CT]), or 2) Magnetic Resonance Imaging (MRI)

An embodiment or approach of the present disclosure provides a complementary drug operation - two drugs in different bubble populations that are stable in isolation but upon ultrasound disruption mix and become active / unstable / therapeutic.

[0120] An embodiment or approach of the present disclosure provides a therapeutic ultrasound plus bubble, drug and stent - wherein ultrasound induces vibrational mode / activity within stent so as to elicit therapeutic effect among cells/ drugs / bubbles adjacent to stent surface.

[0121] An embodiment or approach of the present disclosure provides a different types of stent and different generations of stent - bare metal stent, current DES, dissolving polymer stent, non polymer stent.

[0122] An embodiment or approach of the present disclosure provides an acoustic signature of stent that may be monitored to determine degree of accumulation of stiff acoustic loading on stent and any change resulting from therapeutic effect.

[0123] An embodiment or approach of the present disclosure provides microbubbles that are delivered to a vascular aneurism to deliver a drug that promotes smoothmusclemgration and proliferation toheal the aneurism. Drugs include but are not limited to PDGF-BB, bFGF, etc.

[0124] An embodiment or approach of the present disclosure provides a method for localized drug delivery wherein the drug-carrying bubbles possess a selected molecular attachment ligand - such as VCAM-1, P-Selectin, etc. under realtime ultrasound image guidance including any permutation thereof:

- dual targeting method - fast catch / slow hold [52]
- 3. microbubble composition, for use as in claim 1 and 2 such that a plurality of targeting ligands capa-

ble of binding with the diseased tissue, some of the ligands capable of binding rapidly, and others binding firmly, are attached to the microbubbles.

- variant on bubbles such as liposomes
- nanoparticle + bubble
- Microbubble composition, such as in claim 1, 2 or 3, having liposomes or biocompatible nanoparticles applied to the microbubble shell to house the drug compounds to be released by targeted insonation
- dual modality contrast Ultrasound + MRI contrast Bubble + ferrous (or in another disclosure)
- potential of drug not being integrated in bubble shell but existing in free solution aside the bubbles and relying on bubble related sonoporation to result in preferential drug uptake.

[0125] An embodiment or approach of the present disclosure provides a drug that may be rapamycin ((antiproliferative, immunosuppressive, or antiinflammatory drug, such as rapamycin, tacrolimus, paclitaxel, dexamethasone, or an active analog or derivative, or combinations thereof.).

[0126] An embodiment or approach of the present disclosure provides a subset of relevant bubble properties - dimensions, core gas, shell materials, etc.

[0127] An embodiment or approach of the present disclosure provides a microbubble composition having drug incorporated, situated, dispersed, dissolved therein directly in the shell, core or core multiplicity, or attached to the outside of the shell, having shell(s) comprised with lipids, phospholipids, oils, fats, lipopolymers, polymers, proteins, surfactants or combinations thereof, shell thickness varied from monomolecular 1 nm, to multimolecular and multilamellar, up to and including 1000 nm.

[0128] An embodiment or approach of the present disclosure provides microbubble compositions having internal core filled with the gas, gas-vapor mixture or gas precursor phase, gas having molecular mass from about 10 to about 360.

[0129] An embodiment or approach of the present disclosure provides a microbubble compositions having decafluorobutane core.

[0130] An embodiment or approach of the present disclosure provides an acoustic radiation force is used to translate bubbles towards a selected vessel wall, or other organs or tissues as desired..

[0131] An embodiment or approach of the present disclosure provides an application in the coronary artery, application in other vessels, or other organs or tissues as desired.

[0132] An embodiment or approach of the present disclosure provides a systemic injection of bubbles.

[0133] An embodiment or approach of the present disclosure provides a localized injection of bubbles - from catheter tip -preferably same catheter as imaging but potentially from separate one. See catheter cross-sectional drawing above.

[0134] An embodiment or approach of the present disclosure provides an ultrasound image guidance of bubbles in a highly bubble-specific mode using one of pulse inversion, amplitude scaling ("power modulation") or combination of two ("contrast pulse sequences"):

wherein ultrasound intensity has therapeutic (drug delivery) effect; and/or
wherein ultrasound has cell death effect.

[0135] An embodiment or approach of the present disclosure provides an ultrasound catheter - 1-2 MHz therapeutic, 30 MHz imaging.

[0136] An embodiment or approach of the present disclosure provides a co-located transducer - imaging device overlaying the therapeutic device, imaging device residing in an aperture formed within center of therapeutic device (which may be less desirable than overlaying).

[0137] An embodiment or approach of the present disclosure provides a synchronized operation - the imaging system is "gated" to never operating during the time of therapeutic operation:

wherein the therapeutic system "listens" for imaging system operation and inserts therapeutic pulses between imaging operations, and/or
wherein the imaging system "listens" for therapeutic system operation and inserts imaging pulses between therapeutic operations.

[0138] An embodiment or approach of the present disclosure provides a "Pulse sequence" claims - X seconds (s) of therapeutic, followed by Y s of imaging, and so on for Z minutes (time, repetition, cycles and duration as desired or required).

[0139] An embodiment or approach of the present disclosure provides an integrating of this device on a catheter with other preferred catheter device options - e.g. balloon, pressure measurement, temperature measurement, blood sampling.

[0140] An embodiment or approach of the present disclosure provides a catheter with "over the wire" capability - the standard - has capability to be "threaded" over an in-place metal wire.

[0141] An embodiment or approach of the present disclosure provides a catheter with "over the wire" capability - the standard - has capability to be "threaded" over an in-place metal wire. An embodiment or approach of the present disclosure provides a catheter that is a derivative of the "Volcano" IVUS catheter (phased annular array). A therapeutic transducer - side firing - is placed near to the imaging annular array.

[0142] An embodiment or approach of the present disclosure provides a catheter that is a derivative of the "Boston-Scientific" IVUS catheter (mechanically scanned single element) i.e. the existing high frequency transducer element is replaced with a stack of low frequency (therapeutic) about 1MHz element with about 30 MHz imaging overlaid. Alternatively, there are two transducers side by

side in close proximity. Frequency may vary as desired or required.

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[0143] The devices, systems, and methods of various embodiments disclosed herein may utilize aspects disclosed in the following references, applications, publications and patents:

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[0144] The devices, systems, and methods of various embodiments disclosed herein may utilize aspects disclosed in the following references, applications, publications and patents:

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[0146] It should be appreciated that various sizes, dimensions, contours, rigidity, shapes, flexibility and materials of any of the embodiments discussed throughout may be varied and utilized as desired or required

[0147] It should be appreciated that the related components and subsystems discussed herein may can take on all shapes along the entire continual geometric spectrum of manipulation of x, y and z planes to provide and meet the anatomical and structural demands and requirements. Unless clearly specified to the contrary, there is no requirement for any particular described or illustrated activity or element, any particular sequence or such activities, any particular size, speed, material, duration, contour, dimension or frequency, or any particularly interrelationship of such elements. Moreover, any activity can be repeated, any activity can be performed by multiple entities, and/or any element can be duplicated. Further, any activity or element can be excluded, the sequence of activities can vary, and/or the interrelationship of elements can vary. Accordingly, the invention is to be considered as limited only by the scope of the following claims, including all modifications and equivalents. Still other embodiments will become readily apparent to those skilled in this art from reading the above-recited detailed description and drawings of certain exemplary embodiments. It should be understood that numerous variations, modifications, and additional embodiments are possible, and accordingly, all such variations, modifications, and embodiments are to be regarded as being within the scope of this application. For example, regardless of the content of any portion (e.g., title, field, background, summary, abstract, drawing figure, etc.) of this application, unless clearly specified to the contrary, there is no requirement for the inclusion in any claim herein or of any application claiming priority hereto of any particular described or illustrated activity or element, any particular sequence of such activities, or any particular interrelationship of such elements. Moreover, any activity can be repeated, any activity can be performed by multiple entities, and/or any element can be duplicated. Further, any activity or element can be excluded, the sequence of activities can vary, and/or the interrelationship of elements can vary. Unless clearly specified to the contrary, there is no requirement for any particular described or illustrated activity or element, any particular sequence or such activities, any particular size, speed, material, dimension or frequency, or any particularly interrelationship of such elements. Accordingly, the descriptions and drawings are to be regarded as illustrative in nature, and not as

restrictive. Moreover, when any number or range is described herein, unless clearly stated otherwise, that number or range is approximate. When any range is described herein, unless clearly stated otherwise, that range includes all values therein and all sub ranges therein.

Claims

1. An ultrasound catheter system (102, 402) for providing therapy to a treatment site at one or more locations of a subject (113), the system comprising:

   a tubular member (118, 418) having a proximal region (115) and distal region (117), said distal region being adapted to advance to or in proximity to the subject's (113) treatment site;
   a microbubble reservoir (132) in hydraulic communication with said tubular member (118, 418), said microbubble reservoir (132) is adapted to release microbubbles that are intended to be located into or proximal to the treatment site;
   an ultrasonic energy source (112, 412) in communication with said distal region (117) of said tubular member (118), said ultrasonic energy adapted for:

      imaging the treatment site, and
      rupturing said microbubbles,

   wherein said ultrasonic energy source (112, 412) comprises an ultrasound transducer being disposed within said distal region (117) of said tubular member (118, 418);
   wherein said ultrasound transducer comprises:

      a therapeutic transducer (436) for said rupturing of said microbubbles; and
      an imaging transducer (437) for said imaging of the treatment site;
      wherein said therapeutic transducer (436) and said imaging transducer (437) are stacked, one on top of the other, and form two active layers of said ultrasound transducer, or are configured as a single transducer; and
      control circuitry (100) configured to send electrical activation to said ultrasonic energy source (112, 412).

2. The system of claim 1, wherein the ultrasonic energy emitted for said imaging comprises high frequency energy in the range of about 2 MHz to about 50 MHz.

3. The system of claim 1, wherein the ultrasonic energy emitted for said imaging comprises high frequency energy in the range of about 5 MHz to about 30 MHz.

4. The system of any one of claims 1 to 3, wherein the ultrasonic energy emitted for said rupturing comprises low frequency ultrasound transmission and reception, and high pressure of at least about 20 kPa.

5. The system of claim 4, wherein said high pressure comprises at least about 200 kPa.

6. The system of claim 4, wherein said high pressure comprises at least about 50 kPa.

7. The system of any one of claims 4 to 6, wherein said low frequency comprises a range of about 0.1 MHz to about 10 MHz.

8. The system of any one of claims 4 to 6, wherein said low frequency comprises a range of about 0.2 MHz to about 2 MHz.

9. The system of any one of claims 1 to 8, further comprising:
   an outlet port (433) disposed on said tubular member (118, 418) in communication with said microbubble reservoir (132).

10. The system of any one of claims 1 to 9, further comprising:
    a microfluidic flow-focusing device in communication with at least one of said tubular member (118, 418) and a second tubular member (118, 418) or a lumen in communication with said microbubble reservoir (132), to allow microbubbles to exit from said reservoir, said microfluidic flow focusing device being configured in relation to said microbubble reservoir (132) to translate said microbubbles into or in the vicinity of the treatment site.

11. The system of any one of claims 1 to 10, further comprising said microbubbles, wherein said microbubbles comprise at least one of: a drug composition, an agent composition, a drug and agent composition, or a contrast agent.

12. The system of claim 11, wherein said drug or agent composition, said contrast agent, or said drug and agent composition, being disposed at at least one location comprising:
    in the shell of said microbubbles, in the core or core multiplicity of said microbubbles or outside the shell of said microbubbles.

13. The system of claim 11 or claim 12 , wherein a shell thickness of said microbubbles may vary from monomolecular 1 nm, to multimolecular and multilamellar, up to and including about 1,000 nm.

14. The system of claim 11 or claim 12 , wherein shells forming said microbubbles have a shell thickness

that may vary from monomolecular 0.1 nm, to multimolecular and multilamellar, up to and including about 10,000 nm.

15. The system of any one of claims 11 to 14, wherein said drug composition comprises at least one of the following: antiproliferative, immunosuppressive, or antiinflammatory drug.

16. The system of any one of claims 11 to 14, wherein said drug composition includes at least one drug selected from a group consisting of: actinomycin-D, batimistat, c-myc antisense, dexamethasone, paclitaxel, taxanes, sirolimus, tacrolimus and everolimus, unfractionated heparin, low-molecular weight heparin, enoxaprin, bivalirudin, tyrosine kinase inhibitors, Gleevec, wortmannin, PDGF inhibitors, AG1295, rho kinase inhibitors, Y27632, calcium channel blockers, TRAM-34, IKCa channel blockers, amlodipine, nifedipine, and ACE inhibitors, S1P1 and/or S1P3 receptor antagonists, sphingosine kinase 1 inhibitors, synthetic polysaccharides, ticlopinin, dipyridamole, clopidogrel, fondaparinux, streptokinase, urokinase, r-urokinase, r-prourokinase, rt-PA, APSAC, TNK-rt-PA, reteplase, alteplase, monteplase, lanoplase, pamiteplase, staphylokinase, abciximab, tirofiban, orbofiban, xemilofiban, sibrafiban, roxifiban" an anti-restenosis agent, an anti-thrombogenic agent, an antibiotic, an anti-platelet agent, an anti-clotting agent, an anti-inflammatory agent, an anti-neoplastic agent, a chelating agent, penicillamine, triethylene tetramine dihydrochloride, EDTA, DMSA (succimer), deferoxamine mesylate, a radiocontrast agent, a radio-isotope, a prodrug, antibody fragments, antibodies, gene therapy agents, viral vectors and plasmid DNA vectors.

17. The system of any one of claims 11 to 16, wherein said drug composition comprises coated microbubbles that possess a selected molecular attachment ligand.

18. The system of any one of claims 11 to 17, wherein said microbubbles comprise an internal core filled with the gas, gas-vapor mixture or gas precursor phase, or any combination thereof.

19. The system of any one of claims 11 to 18, wherein said microbubbles comprise a decafluorobutane core.

20. The system of any one of claims 11 to 19, wherein the shells of said microbubbles comprise a gas or mixture of two or more gases or gas precursors.

21. The system of any one of claims 1 to 20, wherein said therapeutic transducer (436) and said imaging transducer (437) are essentially vertically overlaying one another.

22. The system of any one of claims 1 to 20, wherein said therapeutic transducer (436) and said imaging transducer (437) are identical.

23. The system of any one of claims 1 to 22, wherein said controller gates said imaging ultrasonic energy and said rupturing ultrasonic energy, whereby they deliver energy temporally exclusive.

24. The system of any one of claims 1 to 22, wherein said controller gates said imaging ultrasonic energy and said rupturing ultrasonic energy, whereby they deliver energy simultaneously or at least partially simultaneously.

25. The system of any one of claims 1 to 24, further comprising an occlusion device or partial-occlusion device disposed either upstream or downstream from said treatment site and configured to occlude or partially occlude said infused microbubbles.

26. The system of any one of claims 1 to 24, further comprising:

a first occlusion device or partial-occlusion device disposed upstream from said treatment site to occlude or partially occlude said infused microbubbles at said treatment site; and
a second occlusion device or partial-occlusion device disposed downstream from said treatment site and configured to occlude or partially occlude said infused microbubbles at said treatment site.

Patentansprüche

1. Ein Ultraschallkathetersystem (102, 402) zum Bereitstellen einer Therapie an einen Behandlungsort an einer oder mehreren Stellen eines Patienten (113), wobei das System aufweist:

ein rohrförmiges Element (118, 418), aufweisend einen proximalen Bereich (115) und einen distalen Bereich (117), wobei der distale Bereich angepasst ist, um sich zu dem oder in die Nähe des Behandlungsortes des Patienten (113) vorwärtszubewegen,
einen Mikroblasenbehälter (132) in hydraulischer Kommunikation mit dem rohrförmigen Element (118, 418), wobei der Mikroblasenbehälter (132) angepasst ist, um Mikroblasen freizusetzen, die dazu bestimmt sind, in den oder proximal zu dem Behandlungsort positioniert zu werden,
eine Ultraschallenergiequelle (112, 412) in

Kommunikation mit dem distalen Bereich (117) des rohrförmigen Elements (118), wobei die Ultraschallenergie angepasst ist zum:

Abbilden des Behandlungsortes und Aufbrechen der Mikroblasen,

wobei die Ultraschallenergiequelle (112, 412) einen Ultraschallwandler, der innerhalb des distalen Bereichs (117) des rohrförmigen Elements (118, 418) angeordnet ist, aufweist,
wobei der Ultraschallwandler aufweist:

einen Therapiewandler (436) für das Aufbrechen der Mikroblasen und
einen Abbildungswandler (437) für das Abbilden des Behandlungsortes,

wobei der Therapiewandler (436) und der Abbildungswandler (437) einer über den anderen gestapelt sind und zwei aktive Schichten des Ultraschallwandlers ausbilden, oder als ein einziger Wandler konfiguriert sind, und
einen Steuerschaltkreis (100), der konfiguriert ist, um eine elektrische Aktivierung an die Ultraschallenergiequelle (112, 412) zu senden.

2. Das System gemäß Anspruch 1, wobei die zum Abbilden emittierte Ultraschallenergie Hochfrequenzenergie im Bereich von etwa 2 MHz bis etwa 50 MHz aufweist.

3. Das System gemäß Anspruch 1, wobei die zum Abbilden emittierte Ultraschallenergie Hochfrequenzenergie im Bereich von etwa 5 MHz bis etwa 30 MHz aufweist.

4. Das System gemäß irgendeinem der Ansprüche 1 bis 3, wobei die zum Aufbrechen emittierte Ultraschallenergie Niederfrequenz-Ultraschall-Übertragung und -Empfang und Hochdruck von mindestens etwa 20 kPa aufweist.

5. Das System gemäß Anspruch 4, wobei der Hochdruck mindestens etwa 200 kPa aufweist.

6. Das System gemäß Anspruch 4, wobei der Hochdruck mindestens etwa 50 kPa aufweist.

7. Das System gemäß irgendeinem der Ansprüche 4 bis 6, wobei die Niederfrequenz einen Bereich von etwa 0,1 MHz bis etwa 10 MHz aufweist.

8. Das System gemäß irgendeinem der Ansprüche 4 bis 6, wobei die Niederfrequenz einen Bereich von etwa 0,2 MHz bis etwa 2 MHz aufweist.

9. Das System gemäß irgendeinem der Ansprüche 1 bis 8, ferner aufweisend:
eine Auslassöffnung (433), die an dem rohrförmigen Element (118, 418) in Kommunikation mit dem Mikroblasenbehälter (132) angeordnet ist.

10. Das System gemäß irgendeinem der Ansprüche 1 bis 9, ferner aufweisend:
eine Mikrofluidikströmungs-Fokussiervorrichtung in Kommunikation mit mindestens einem von dem rohrförmigen Element (118, 418) und einem zweiten rohrförmigen Element (118, 418) oder ein Lumen in Kommunikation mit dem Mikroblasenbehälter (132), um zu ermöglichen, dass Mikroblasen aus dem Behälter austreten, wobei die Mikrofluidikströmungs-Fokussiervorrichtung im Verhältnis zu dem Mikroblasenbehälter (132) konfiguriert ist, um die Mikroblasen in den oder in die Umgebung des Behandlungsortes zu übertragen.

11. Das System gemäß irgendeinem der Ansprüche 1 bis 10, ferner aufweisend die Mikroblasen, wobei die Mikroblasen mindestens eines von einer Arzneimittelzusammensetzung, einer Wirkstoffzusammensetzung, einer Arzneimittel- und Wirkstoffzusammensetzung oder einem Kontrastmittel aufweisen.

12. Das System gemäß Anspruch 11, wobei die Arzneimittel- oder Wirkstoffzusammensetzung, das Kontrastmittel oder die Arzneimittel- und Wirkstoffzusammensetzung an mindestens einer Stelle angeordnet sind, die aufweist:
in der Hülle der Mikroblasen, im Kern oder in der Kernvielzahl der Mikroblasen oder außerhalb der Hülle der Mikroblasen.

13. Das System gemäß Anspruch 11 oder Anspruch 12, wobei eine Hüllendicke der Mikroblasen von monomolekular 1 nm bis multimolekular und multilamellar, bis zu und einschließlich etwa 1000 nm variieren kann.

14. Das System gemäß Anspruch 11 oder Anspruch 12, wobei Hüllen, die die Mikroblasen ausbilden, eine Hüllendicke haben, die von monomolekular 0,1 nm bis multimolekular und multilamellar, bis zu und einschließlich 10000 nm variieren kann.

15. Das System gemäß irgendeinem der Ansprüche 11 bis 14, wobei die Arzneimittelzusammensetzung mindestens eines von den folgenden aufweist: antiproliferatives, immunsuppressives oder antiinflammatorisches Arzneimittel.

16. Das System gemäß irgendeinem der Ansprüche 11 bis 14, wobei die Arzneimittelzusammensetzung mindestens ein Arzneimittel aufweist, das aus einer Gruppe bestehend aus: Actinomycin D, Batimistat, c-Myc-Antisense, Dexamethason, Paclitaxel, Taxa-

nen, Sirolimus, Tacrolimus und Everolimus, unfraktioniertem Heparin, Heparin mit niedrigem Molekulargewicht, Enoxaparin, Bivalirudin, Tyrosinkinase-Inhibitoren, Gleevec, Wortmannin, PDGF-Inhibitoren, AG1295, Rho-Kinase-Hemmern, Y27632, Calciumkanalblockern, TRAM-34, IKCa-Kanalblockern, Amlodipin, Nifedipin und ACE-Hemmern, S1P1- und/oder S1P3-Rezeptorantagonisten, Sphingosinkinase 1 Inhibitoren, synthetischen Polysacchariden, Ticlopinin, Dipyridamol, Clopidogrel, Fondaparinux, Streptokinase, Urokinase, r-Urokinase, r-Prourokinase, rt-PA, APSAC, TNK-rt-Pa, Reteplase, Alteplase, Monteplase, Lanoplase, Pamiteplase, Staphylokinase, Abciximab, Tirofiban, Orbofiban, Xemilofiban, Sibrafiban, Roxifiban, einem Anti-Restenosemittel, einem antithrombogenen Stoff, einem Antibiotikum, einem Thrombozytenaggregationshemmer, einem gerinnungshemmenden Mittel, einem antiinflammatorischen Mittel, einem antineoplastischen Mittel, einem Chelatbildner, Penicillamin, Triethylentetramin-Dihydrochlorid, EDTA, DMSA (Succimer), Deferoxaminmesylat, einem Röntgenkontrastmittel, einem Radioisotop, einem Prodrug, Antikörperfragmenten, Antikörpern, Gentherapie-Mitteln, viralen Vektoren und Plasmid-DNA-Vektoren ausgewählt ist.

17. Das System gemäß irgendeinem der Ansprüche 11 bis 16, wobei die Arzneimittelzusammensetzung beschichtete Mikroblasen aufweist, die einen ausgewählten Molekulare-Anlagerung-Liganden aufweisen.

18. Das System gemäß irgendeinem der Ansprüche 11 bis 17, wobei die Mikroblasen einen inneren Kern, der mit Gas, Gas-Dampf-Gemisch oder Gasvorläuferphase oder irgendeiner Kombination davon gefüllt ist.

19. Das System gemäß irgendeinem der Ansprüche 11 bis 18, wobei die Mikroblasen einen Decafluorbutan-Kern aufweisen.

20. Das System gemäß irgendeinem der Ansprüche 11 bis 19, wobei die Hüllen der Mikroblasen ein Gas oder ein Gemisch von zwei oder mehr Gasen oder Gasvorläufern aufweisen.

21. Das System gemäß irgendeinem der Ansprüche 1 bis 20, wobei der Therapiewandler (436) und der Abbildungswandler (437) im Wesentlichen vertikal übereinanderliegen.

22. Das System gemäß irgendeinem der Ansprüche 1 bis 20, wobei der Therapiewandler (436) und der Abbildungswandler (437) identisch sind.

23. Das System gemäß irgendeinem der Ansprüche 1 bis 22, wobei die Steuerung die Abbildungsultraschallenergie und die Aufbrech-Ultraschallenergie ansteuert, wodurch diese Energie zeitlich ausschließlich bereitstellen.

24. Das System gemäß irgendeinem der Ansprüche 1 bis 22, wobei die Steuereinrichtung die Abbildungsultraschallenergie und die Aufbrech-Ultraschallenergie ansteuert, wodurch diese Energie gleichzeitig oder zumindest teilweise gleichzeitig bereitstellen.

25. Das System gemäß irgendeinem der Ansprüche 1 bis 24, ferner aufweisend eine Verschlussvorrichtung oder Teilverschlussvorrichtung, die entweder stromaufwärts oder stromabwärts von dem Behandlungsort angeordnet ist und konfiguriert ist, um die infundierten Mikroblasen zu verschließen oder teilweise zu verschließen.

26. Das System gemäß irgendeinem der Ansprüche 1 bis 24, ferner aufweisend:

eine erste Verschlussvorrichtung oder Teilverschlussvorrichtung, die stromaufwärts von dem Behandlungsort angeordnet ist, um die infundierten Mikroblasen an dem Behandlungsort zu verschließen oder teilweise zu verschließen, und
eine zweite Verschlussvorrichtung oder Teilverschlussvorrichtung, die stromabwärts von dem Behandlungsort angeordnet ist und konfiguriert ist, um die infundierten Mikroblasen an dem Behandlungsort zu verschließen oder teilweise zu verschließen.

Revendications

1. Système de cathéter ultrasonore (102, 402) permettant d'administrer une thérapie à un site de traitement à un ou plusieurs emplacements chez un sujet (113), le système comprenant:

un élément tubulaire (118, 418) doté d'une région proximale (115) et d'une région distale (117), ladite région distale étant adaptée pour avancer jusqu'au site de traitement du sujet (113) ou à proximité de celui-ci ;
un réservoir de microbulles (132) en communication hydraulique avec ledit élément tubulaire (118, 418), ledit réservoir de microbulles (132) étant adapté pour libérer des microbulles qui sont destinées à se situer dans le site de traitement ou à proximité de celui-ci ;
une source d'énergie ultrasonore (112, 412) en communication avec ladite région distale (117) dudit élément tubulaire (118), ladite énergie ultrasonore étant adaptée pour :

former des images du site de traitement, et rompre lesdites microbulles,
dans lequel ladite source d'énergie ultrasonore (112, 412) comprend un transducteur ultrasonore disposé dans ladite région distale (117) dudit élément tubulaire (118, 418) ;

dans lequel ledit transducteur ultrasonore comprend :

un transducteur thérapeutique (436) pour ladite rupture desdites microbulles ; et
un transducteur d'imagerie (437) pour ladite formation d'images du site de traitement ;
dans lequel ledit transducteur thérapeutique (436) et ledit transducteur d'imagerie (437) sont empilés l'un sur l'autre et forment deux couches actives dudit transducteur ultrasonore, ou sont configurés comme un transducteur unique ; et
un circuit de commande (100) configuré pour envoyer une activation électrique à ladite source d'énergie ultrasonore (112, 412).

2. Système selon la revendication 1, dans lequel l'énergie ultrasonore émise pour ladite formation d'images comprend une énergie à haute fréquence dans la plage d'environ 2 MHz à environ 50 MHz.

3. Système selon la revendication 1, dans lequel l'énergie ultrasonore émise pour ladite formation d'images comprend une énergie à haute fréquence dans la plage d'environ 5 MHz à environ 30 MHz.

4. Système selon l'une quelconque des revendications 1 à 3, dans lequel l'énergie ultrasonore émise pour ladite rupture comprend une transmission et une réception ultrasonores à basse fréquence, et une haute pression d'au moins environ 20 kPa.

5. Système selon la revendication 4, dans lequel ladite haute pression comprend au moins environ 200 kPa.

6. Système selon la revendication 4, dans lequel ladite haute pression comprend au moins environ 50 kPa.

7. Système selon l'une quelconque des revendications 4 à 6, dans lequel ladite basse fréquence comprend une plage d'environ 0,1 MHz à environ 10 MHz.

8. Système selon l'une quelconque des revendications 4 à 6, dans lequel ladite basse fréquence comprend une plage d'environ 0,2 MHz à environ 2 MHz.

9. Système selon l'une quelconque des revendications 1 à 8, comprenant en outre :
un orifice de sortie (433) disposé sur ledit élément tubulaire (118, 418) en communication avec ledit réservoir de microbulles (132).

10. Système selon l'une quelconque des revendications 1 à 9, comprenant en outre :
un dispositif de concentration d'écoulement microfluidique en communication avec au moins l'un parmi ledit élément tubulaire (118, 418) et un second élément tubulaire (118, 418) ou une lumière en communication avec ledit réservoir de microbulles (132), pour permettre aux microbulles de sortir dudit réservoir, ledit dispositif de concentration d'écoulement microfluidique étant configuré en liaison avec ledit réservoir de microbulles (132) pour déplacer lesdites microbulles jusqu'à l'intérieur du site de traitement ou à proximité de celui-ci.

11. Système selon l'une quelconque des revendications 1 à 10, comprenant en outre lesdites microbulles, dans lequel lesdites microbulles comprennent au moins l'un des éléments suivants : une composition de médicament, une composition d'agent, une composition de médicament et d'agent, ou un agent de contraste.

12. Système selon la revendication 11, dans lequel ladite composition de médicament ou d'agent, ledit agent de contraste ou ladite composition de médicament et d'agent, sont disposés à au moins un emplacement parmi :
l'intérieur de l'enveloppe desdites microbulles, l'intérieur du coeur ou de la multitude de coeurs desdites microbulles ou l'extérieur de l'enveloppe desdites microbulles.

13. Système selon la revendication 11 ou la revendication 12, dans lequel une épaisseur d'enveloppe desdites microbulles peut varier d'une dimension monomoléculaire de 1 nm, à une dimension multimoléculaire et multilamellaire, jusqu'à et y compris une dimension d'environ 1000 nm.

14. Système selon la revendication 11 ou la revendication 12, dans lequel les enveloppes formant lesdites microbulles ont une épaisseur d'enveloppe qui peut varier d'une dimension monomoléculaire de 0,1 nm, à une dimension multimoléculaire et multilamellaire, jusqu'à et y compris une dimension d'environ 10 000 nm.

15. Système selon l'une quelconque des revendications 11 à 14, dans lequel ladite composition de médicament comprend au moins l'un des médicaments suivants : un médicament antiprolifératif, un immunosuppresseur ou un anti-inflammatoire.

16. Système selon l'une quelconque des revendications

11 à 14, dans lequel ladite composition de médicament comprend au moins un médicament choisi dans le groupe constitué des éléments suivants : l'actinomycine D, le batimistat, le c-myc antisens, la dexaméthasone, le paclitaxel, les taxanes, le sirolimus, le tacrolimus, l'évérolimus, l'héparine non fractionnée, l'héparine de faible poids moléculaire, l'enoxaprine, la bivalirudine, les inhibiteurs des tyrosine-kinases, le Gleevec, la wortmannine, les inhibiteurs du PDGF, l'AG1295, les inhibiteurs de la rho-kinase, l'Y27632, les bloqueurs des canaux calciques, le TRAM-34, les bloqueurs des canaux IKCa, l'amlodipine, la nifédipine et les inhibiteurs de l'ECA, les antagonistes des récepteurs S1P1 et/ou S1P3, les inhibiteurs de la sphingosine kinase 1, les polysaccharides synthétiques, la ticlopinine, le dipyridamole, le clopidogrel, le fondaparinux, la streptokinase, l'urokinase, la r-urokinase, la r-prourokinase, le rt-PA, l'APSAC, le TNK-rt-PA, la rétéplase, l'altéplase, la montéplase, la lanoplase, la pamitéplase, la staphylokinase, l'abciximase, le tirofiban, l'orbofiban, le xémilofiban, le sibrafiban, le roxifiban, un agent anti-resténose, un agent antithrombogène, un antibiotique, un agent antiplaquettaire, un agent anticoagulant, un agent anti-inflammatoire, un agent anti-néoplasique, un agent chélatant, la pénicillamine, le dichlorhydrate de triéthylènetétramine, l'EDTA, le DMSA (succimère), le mésylate de déféroxamine, un agent de radiocontraste, un radio-isotope, un promédicament, les fragments d'anticorps, les anticorps, les agents de thérapie génique, les vecteurs viraux et les vecteurs d'ADN plasmidique.

17. Système selon l'une quelconque des revendications 11 à 16, dans lequel ladite composition de médicament comprend des microbulles enrobées qui possèdent un ligand de liaison moléculaire sélectionné.

18. Système selon l'une quelconque des revendications 11 à 17, dans lequel lesdites microbulles comprennent un coeur interne rempli de gaz, d'un mélange de gaz et de vapeur ou d'une phase de précurseur gazeux, ou d'une combinaison quelconque de ces éléments.

19. Système selon l'une quelconque des revendications 11 à 18, dans lequel lesdites microbulles comprennent un coeur de décafluorobutane.

20. Système selon l'une quelconque des revendications 11 à 19, dans lequel les enveloppes desdites microbulles comprennent un gaz ou un mélange d'au moins deux gaz ou précurseurs gazeux.

21. Système selon l'une quelconque des revendications 1 à 20, dans lequel ledit transducteur thérapeutique (436) et ledit transducteur d'imagerie (437) sont superposés l'un sur l'autre de façon essentiellement verticale.

22. Système selon l'une quelconque des revendications 1 à 20, dans lequel ledit transducteur thérapeutique (436) et ledit transducteur d'imagerie (437) sont identiques.

23. Système selon l'une quelconque des revendications 1 à 22, dans lequel ledit dispositif de commande déclenche ladite énergie ultrasonore d'imagerie et ladite énergie ultrasonore de rupture, de sorte qu'elles délivrent de l'énergie temporellement exclusive.

24. Système selon l'une quelconque des revendications 1 à 22, dans lequel ledit dispositif de commande déclenche ladite énergie ultrasonore d'imagerie et ladite énergie ultrasonore de rupture, de sorte qu'elles délivrent de l'énergie de manière simultanée ou au moins en partie simultanée.

25. Système selon l'une quelconque des revendications 1 à 24, comprenant en outre un dispositif d'occlusion ou un dispositif d'occlusion partielle disposé en amont ou en aval dudit site de traitement et configuré pour occlure ou occlure partiellement lesdites microbulles infusées.

26. Système selon l'une quelconque des revendications 1 à 24, comprenant en outre :

un premier dispositif d'occlusion ou dispositif d'occlusion partielle disposé en amont dudit site de traitement pour occlure ou occlure partiellement lesdites microbulles infusées au niveau dudit site de traitement ; et
un second dispositif d'occlusion ou dispositif d'occlusion partielle disposé en aval dudit site de traitement et configuré pour occlure ou occlure partiellement lesdites microbulles infusées au niveau dudit site de traitement.

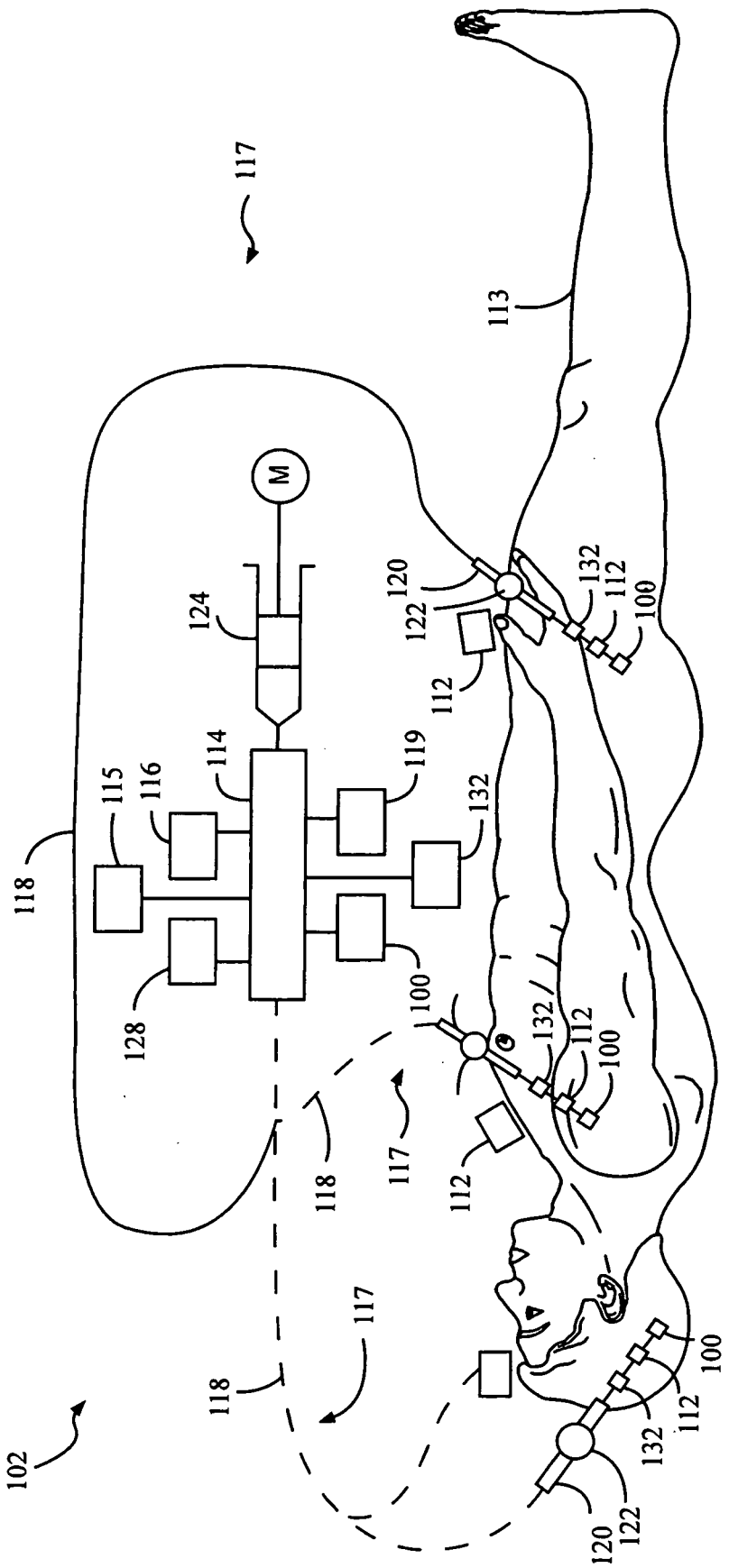

117
113
M
124
114
115
116
118
119
132
128
120
122
112
100
132
112
100
118
117
112
100
132
112
100
118
117
102
120
122
132
112
100

FIG.1

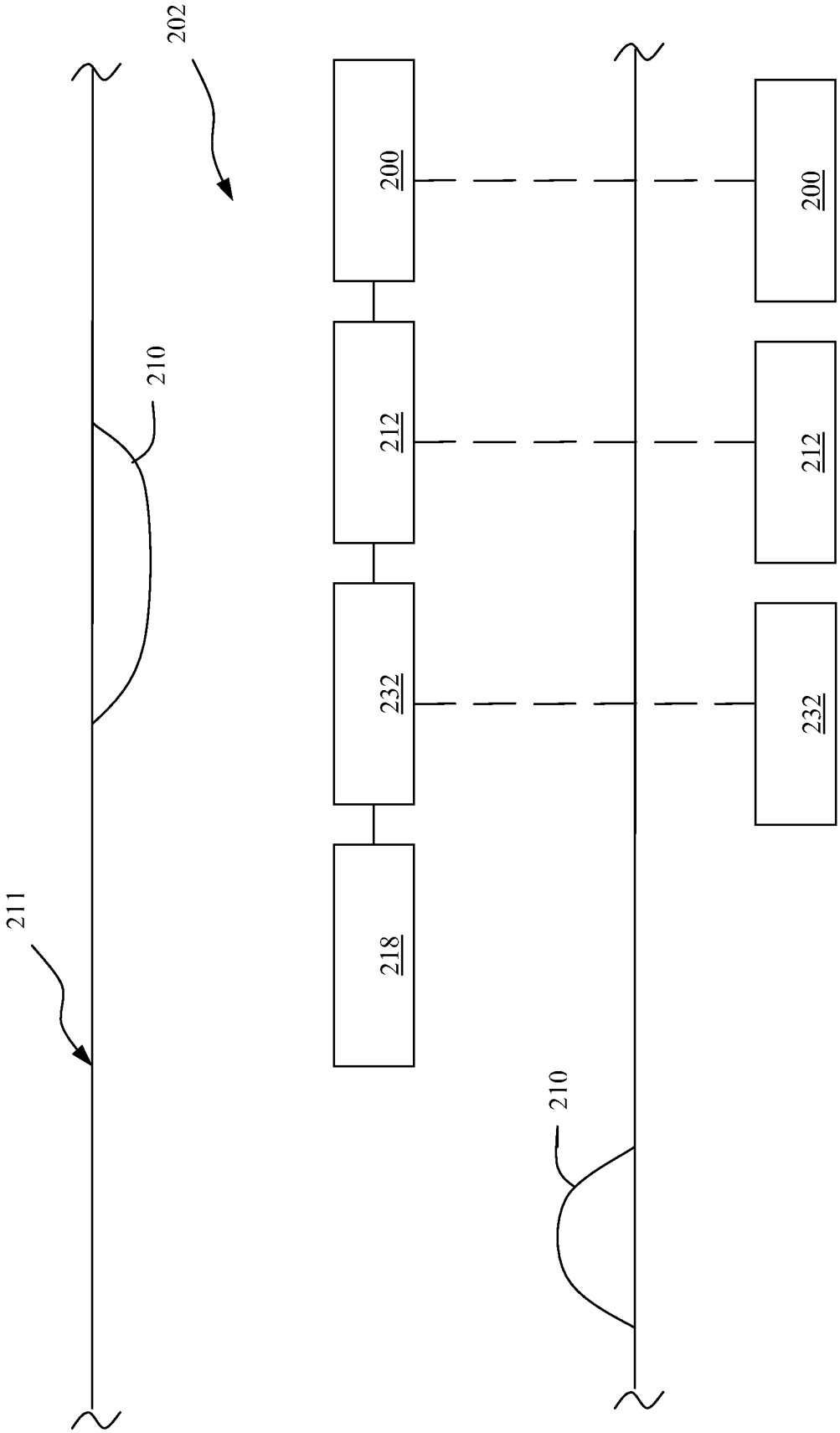


FIG. 2A

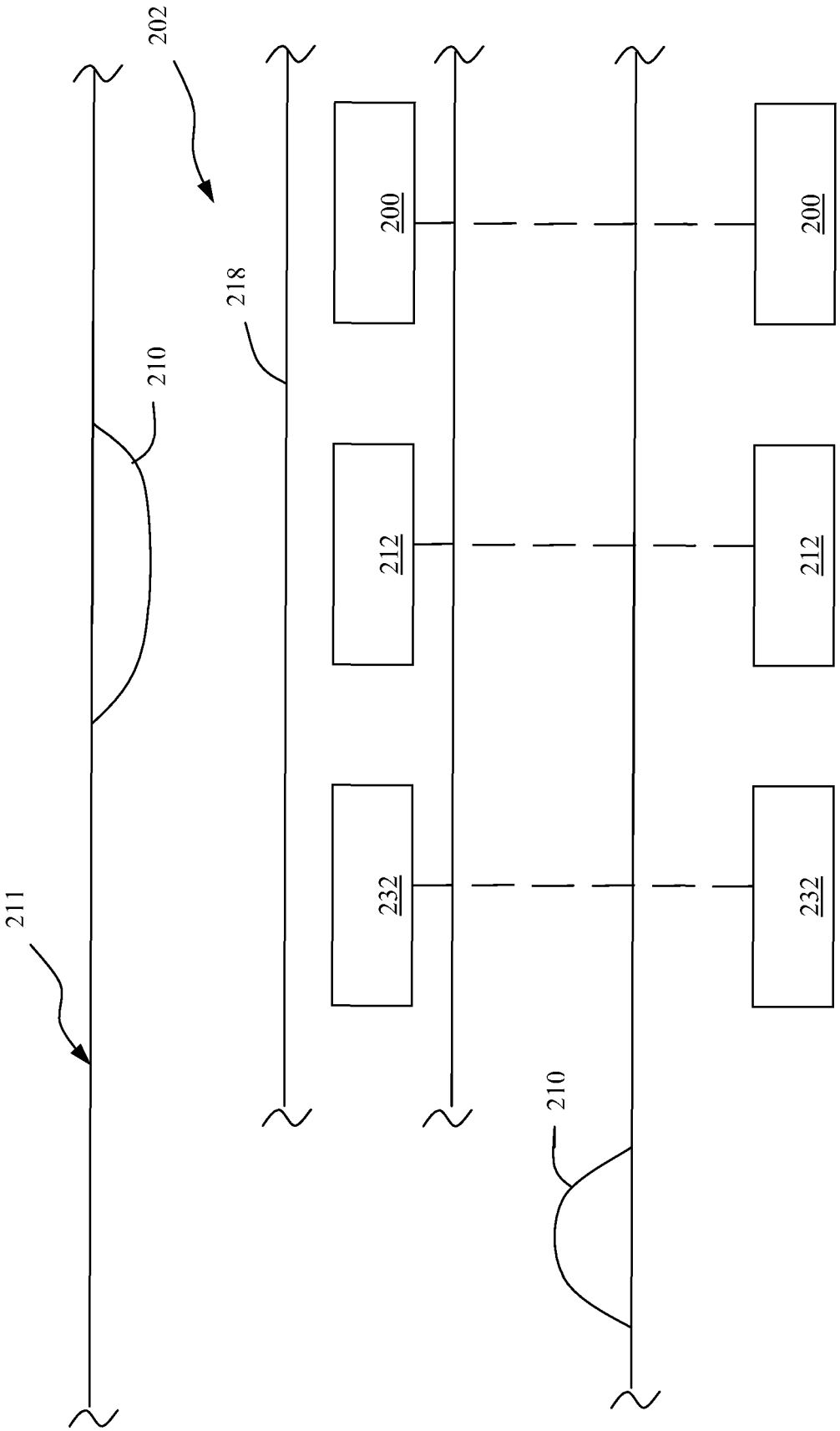


FIG. 2B

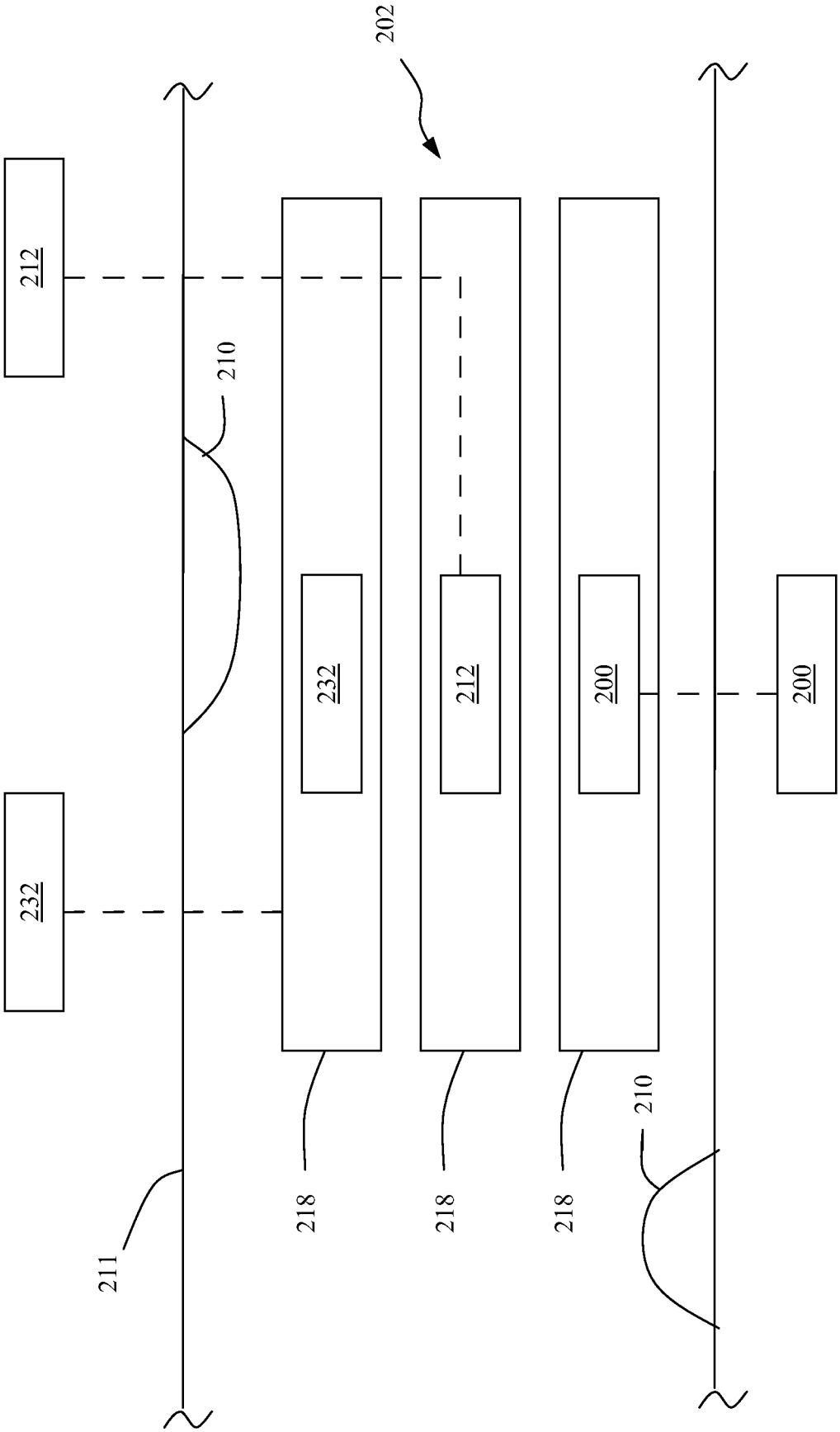


FIG. 2C

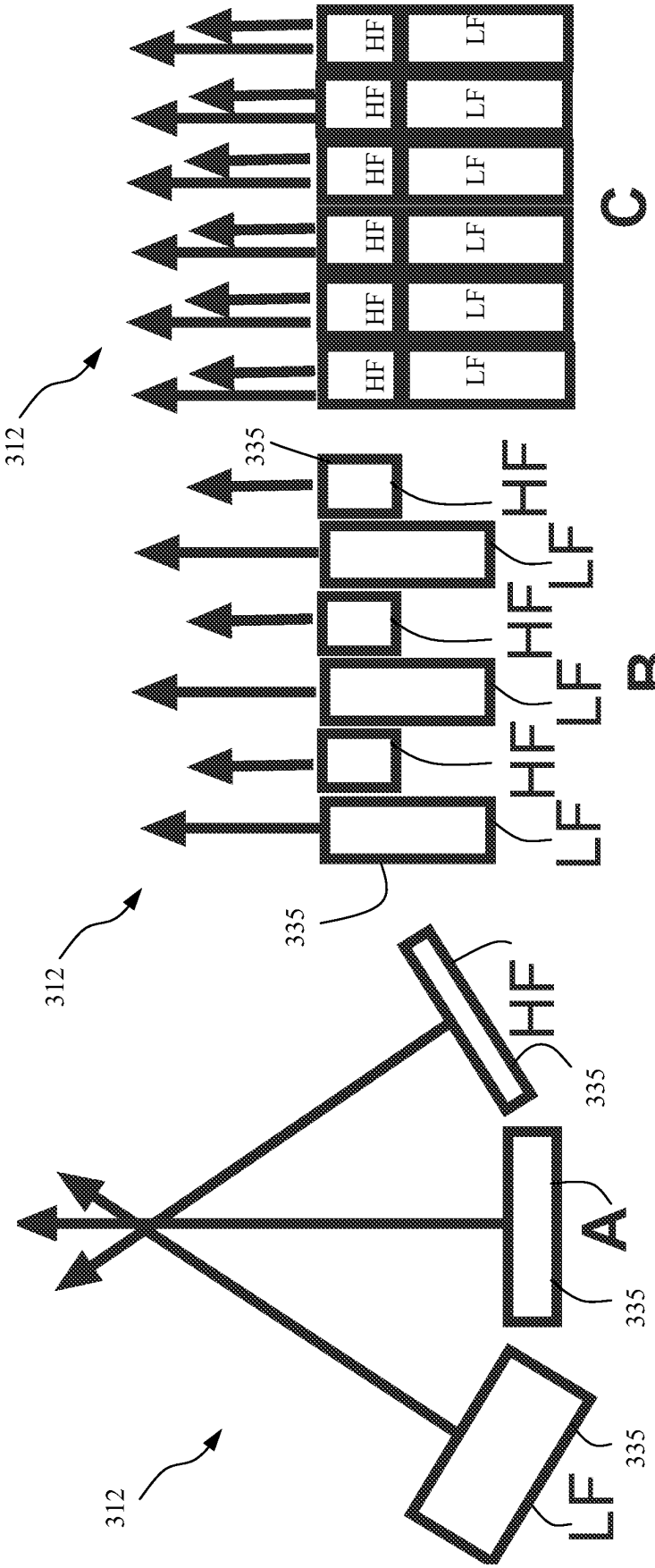


FIG. 3A

FIG. 3B

FIG. 3C

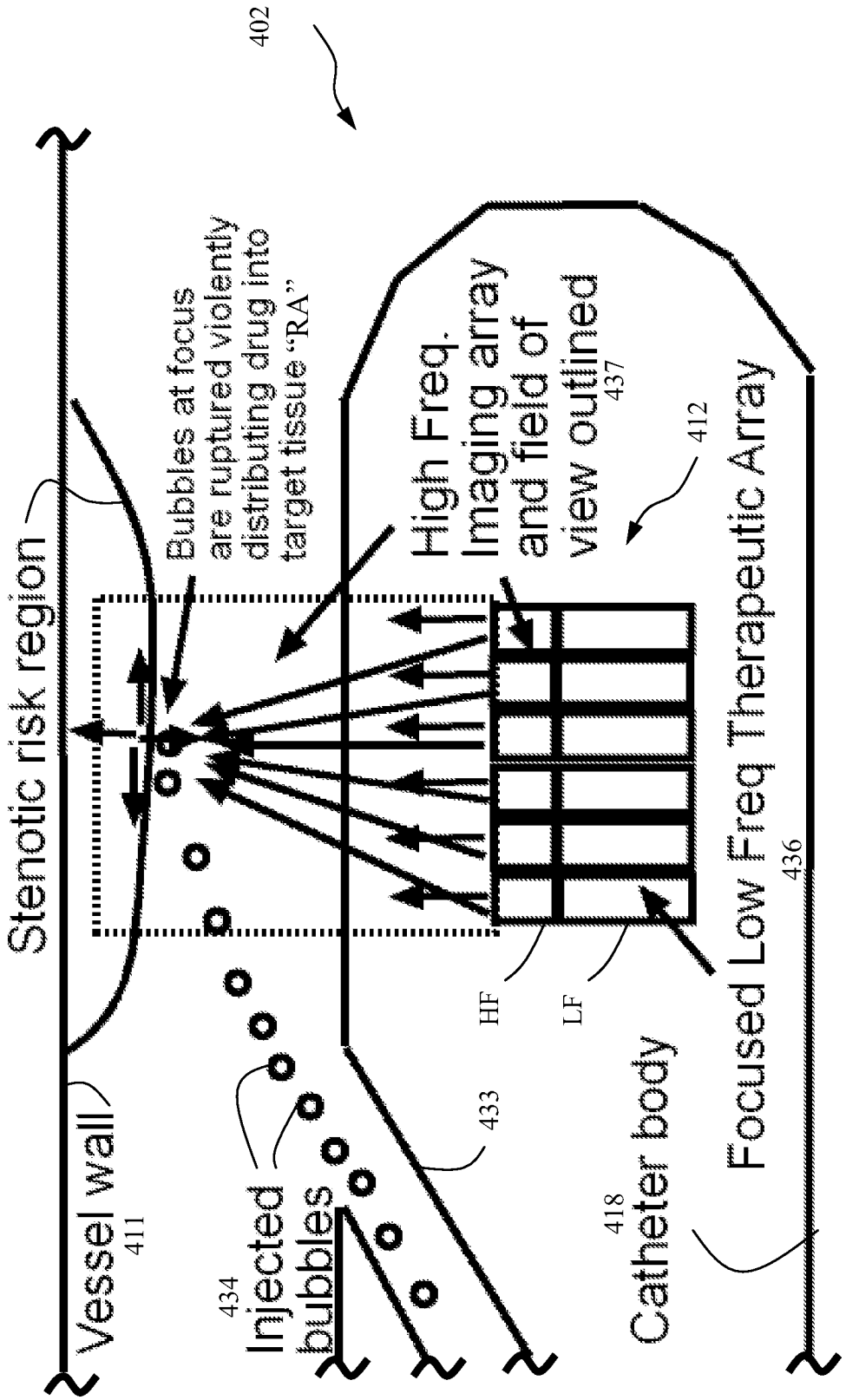

402
Stenotic risk region
410
Bubbles at focus are ruptured violently distributing drug into target tissue "RA"
High Freq. Imaging array and field of view outlined
437
412
Vessel wall
411
433
HF
LF
Injected bubbles
434
Catheter body
418
Focused Low Freq Therapeutic Array
436

FIG. 4

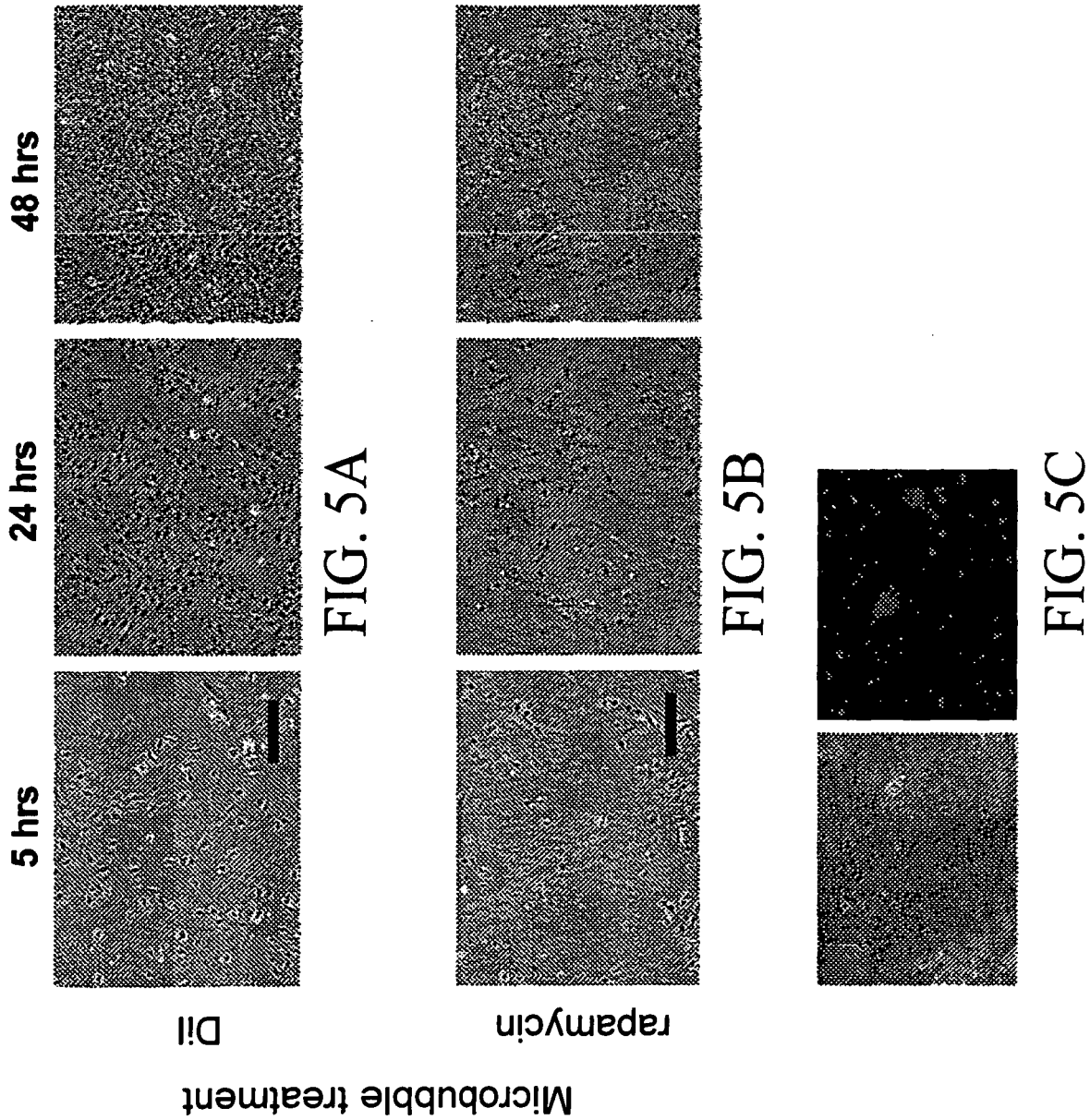


FIG. 5A

FIG. 5B

FIG. 5C

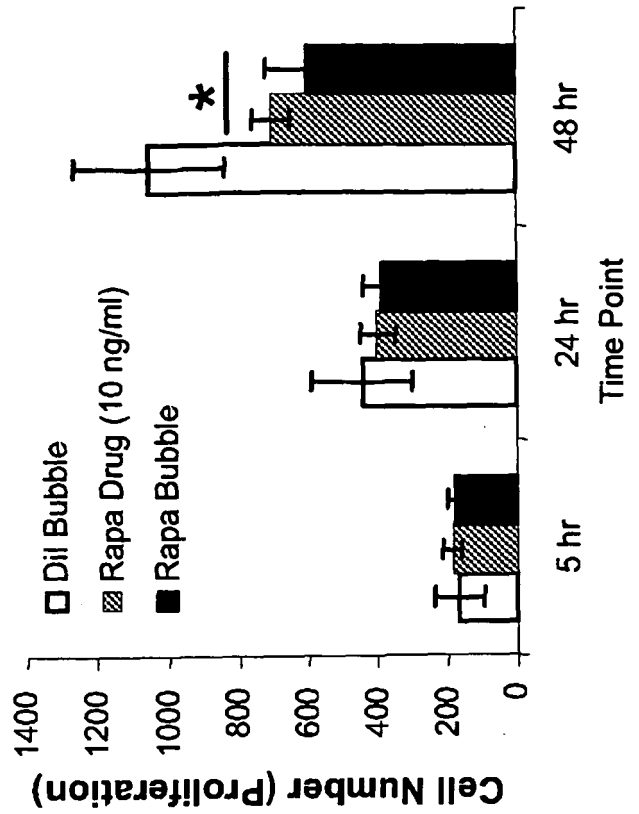

Cell Number (Proliferation)
1400
1200
1000
800
600
400
200
0
Dil Bubble
Rapa Drug (10 ng/ml)
Rapa Bubble
*
5 hr
24 hr
48 hr
Time Point

FIG. 5E

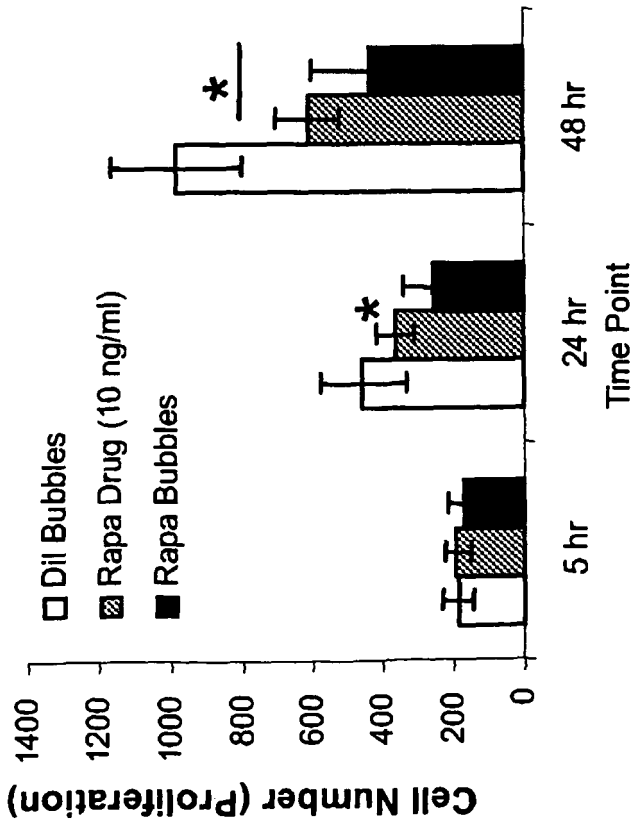

Cell Number (Proliferation)
1400
1200
1000
800
600
400
200
0
Dil Bubbles
Rapa Drug (10 ng/ml)
Rapa Bubbles
*
*
5 hr
24 hr
48 hr
Time Point

FIG. 5D

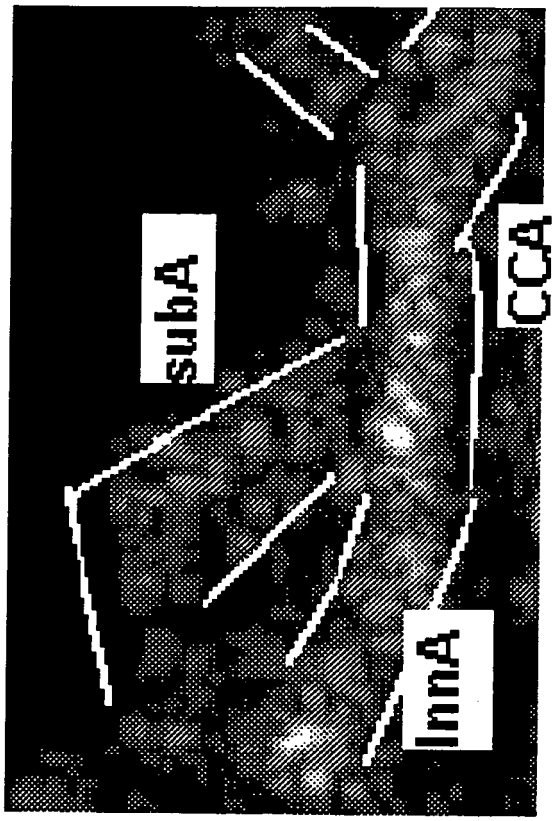


FIG. 6

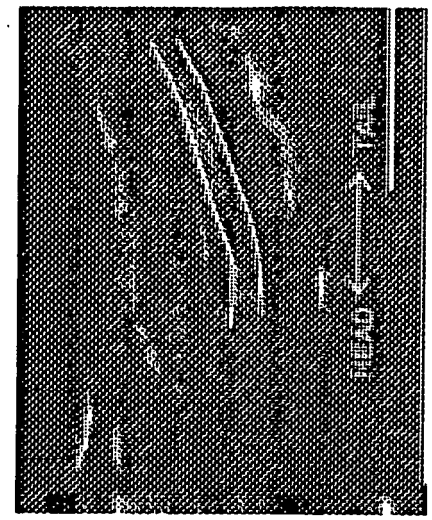


FIG. 7C

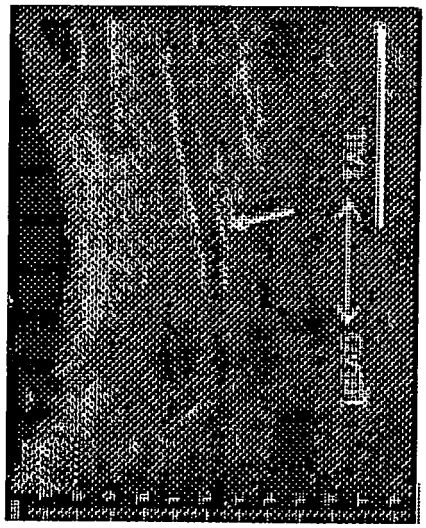


FIG. 7B

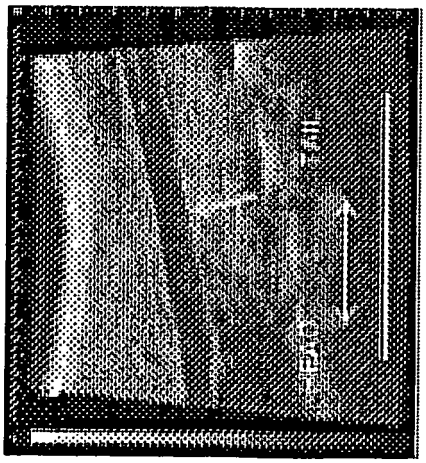


FIG. 7A

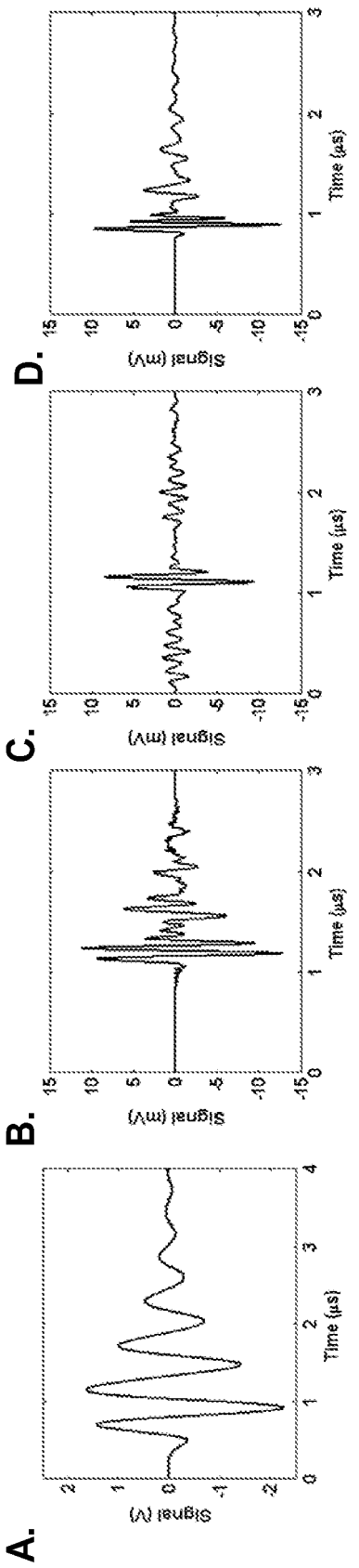

A.
Signal (V)
Time (µs)
B.
Signal (mV)
Time (µs)
C.
Signal (mV)
Time (µs)
D.
Signal (mV)
Time (µs)

FIG. 8

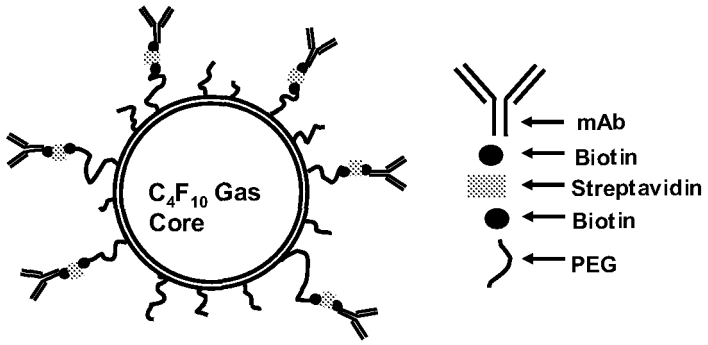

C_4F_{10} Gas Core
mAb
Biotin
Streptavidin
Biotin
PEG

FIG. 9

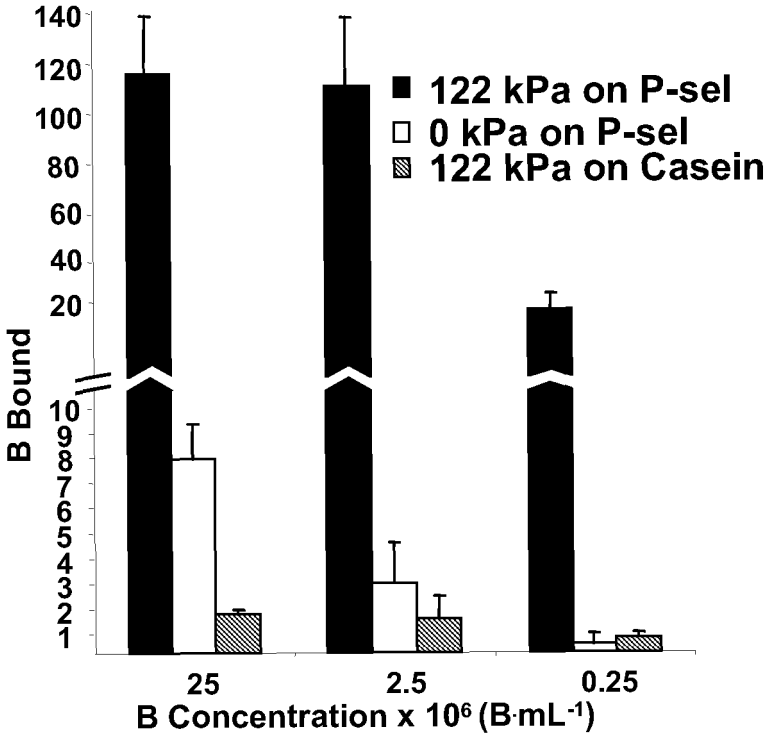

B Bound
140
120
100
80
60
40
20
10
9
8
7
6
5
4
3
2
1
122 kPa on P-sel
0 kPa on P-sel
122 kPa on Casein
25
2.5
0.25
B Concentration x 10^6 ($B \cdot mL^{-1}$)

FIG. 10

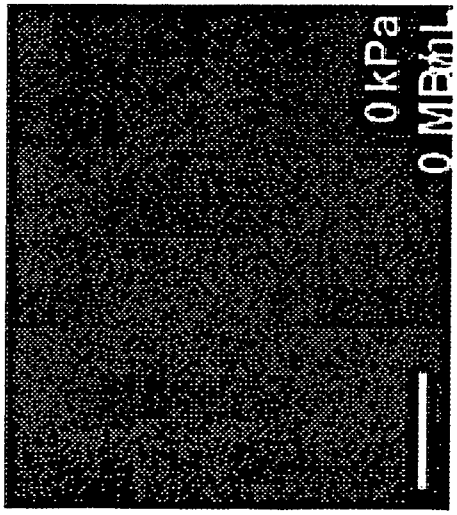


FIG. 11A

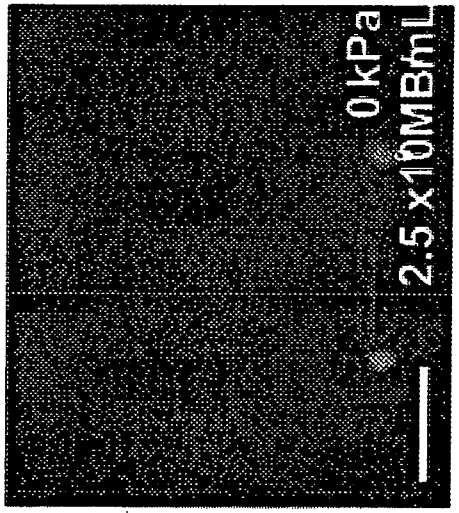


FIG. 11B

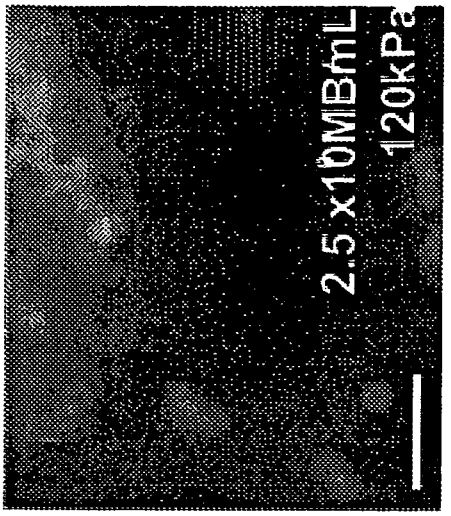


FIG. 11C

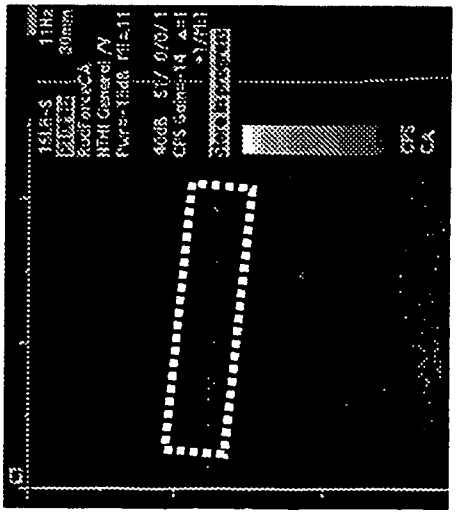


FIG. 11D

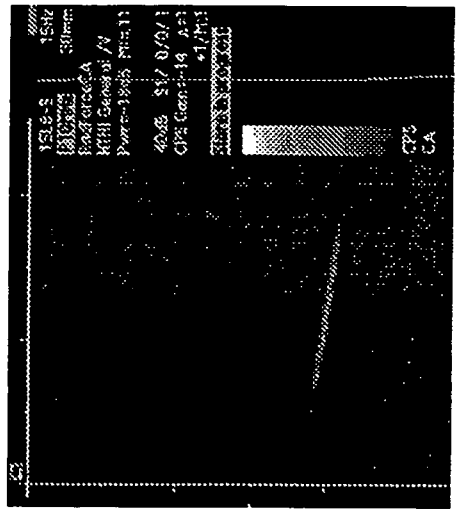


FIG. 11E

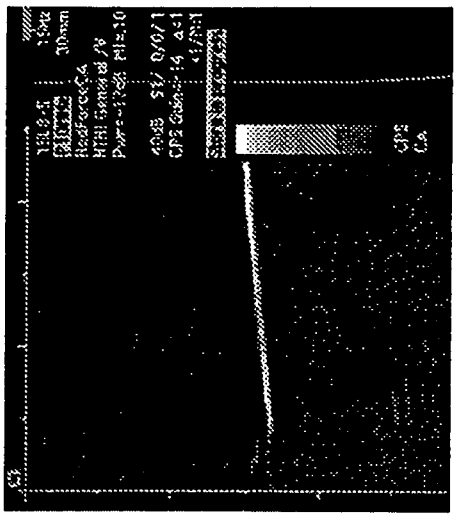


FIG. 11F

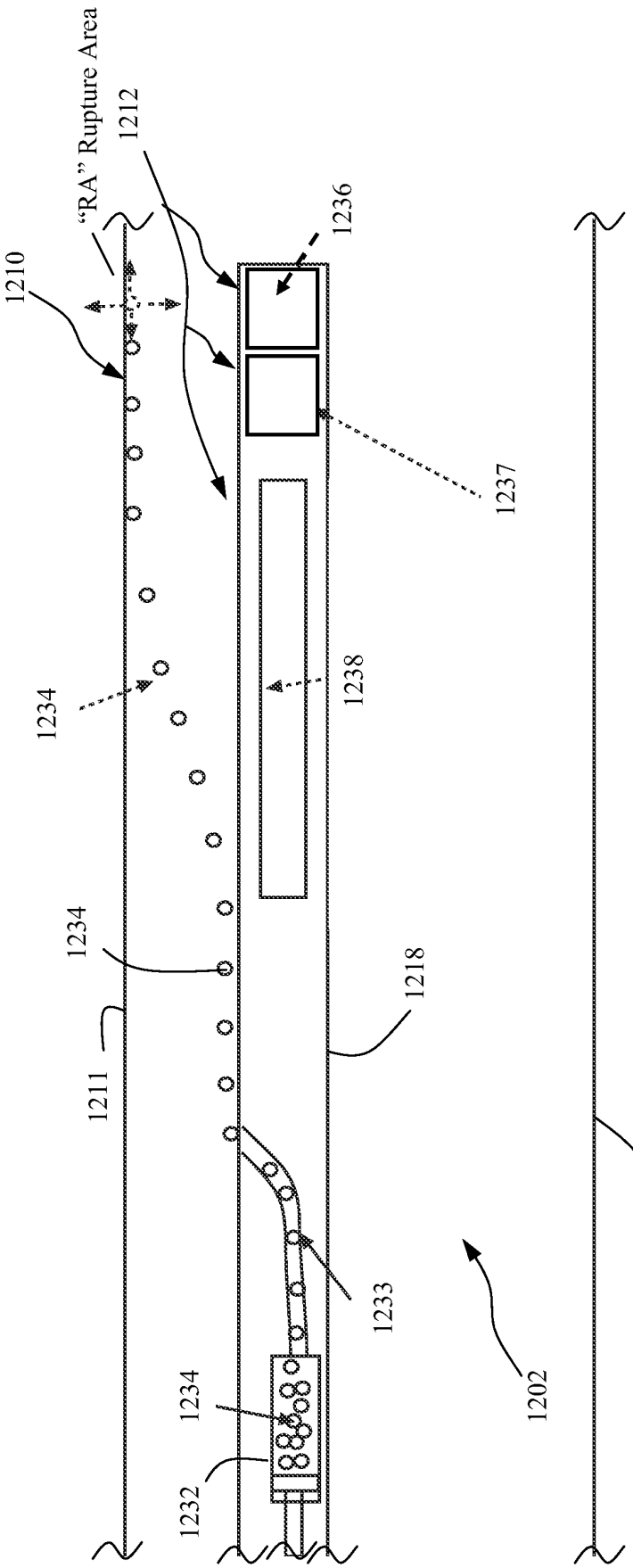

"RA" Rupture Area
1212
1236
1210
1237
1238
1234
1234
1218
1211
1233
1234
1232
1202
1211

FIG. 12A

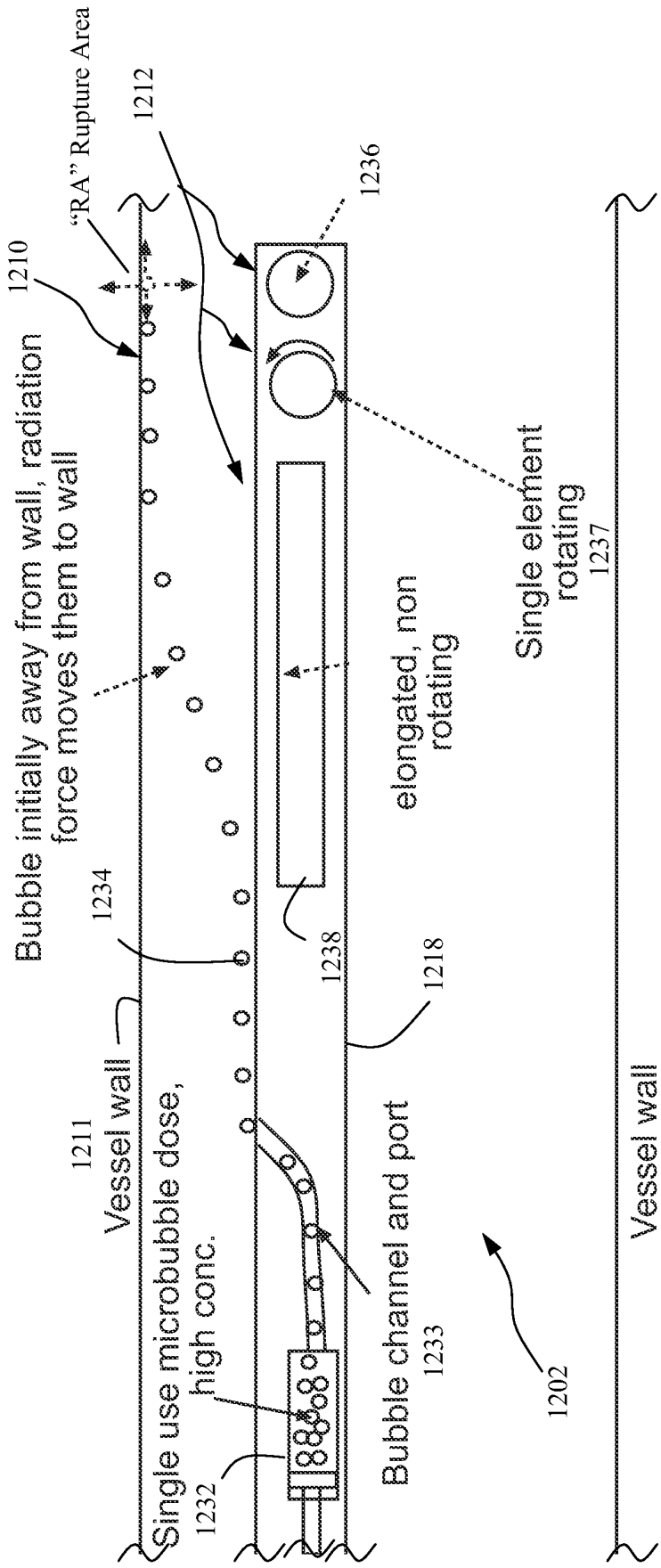

"RA" Rupture Area
1212
1236
1210
Bubble initially away from wall, radiation force moves them to wall
1234
1211
Vessel wall
Single use microbubble dose, high conc.
1232
1238
1218
elongated, non rotating
Single element rotating
1237
Bubble channel and port
1233
1202
Vessel wall
1211

FIG. 12B

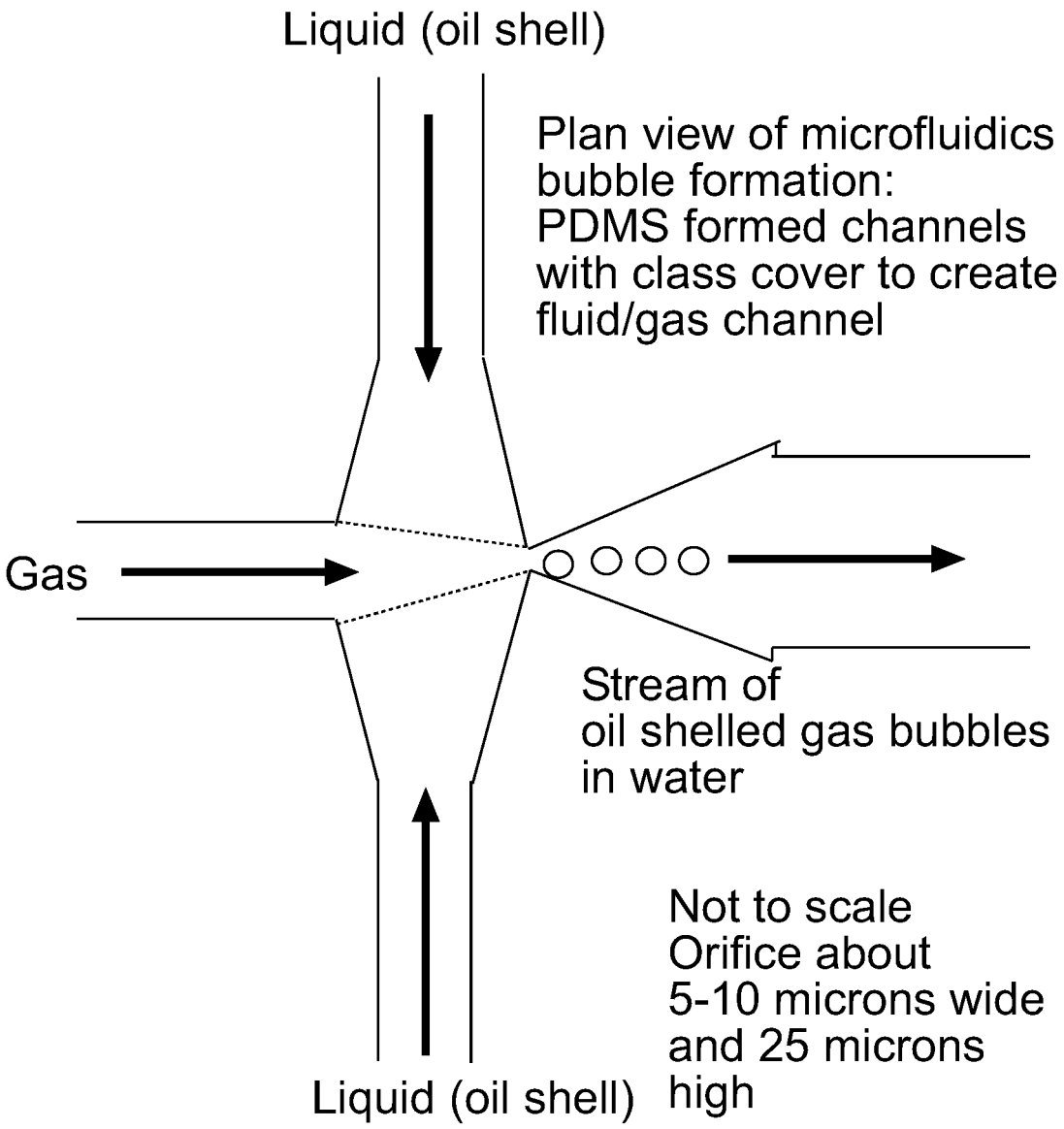

Liquid (oil shell)
Plan view of microfluidics bubble formation:
PDMS formed channels with class cover to create fluid/gas channel
Gas
Stream of oil shelled gas bubbles in water
Not to scale
Orifice about 5-10 microns wide and 25 microns high
Liquid (oil shell)

FIG. 13

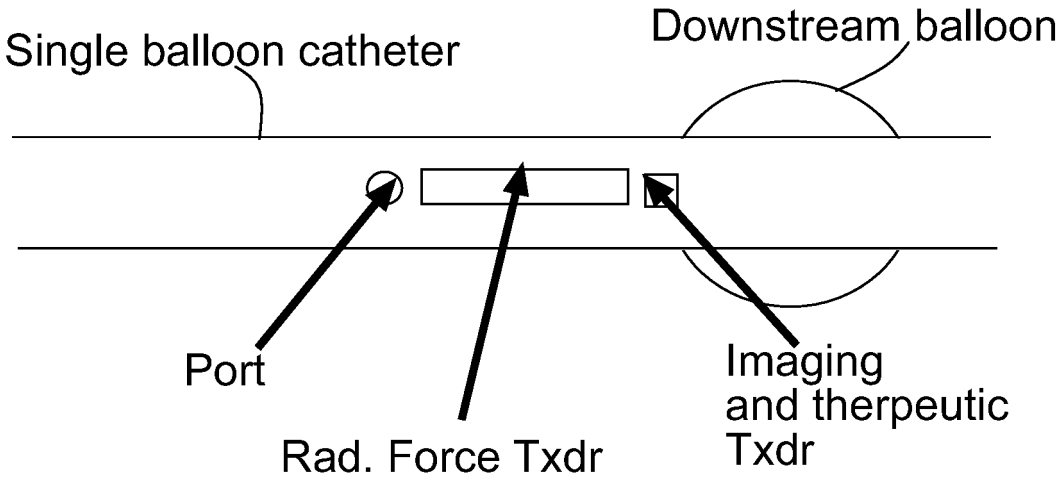
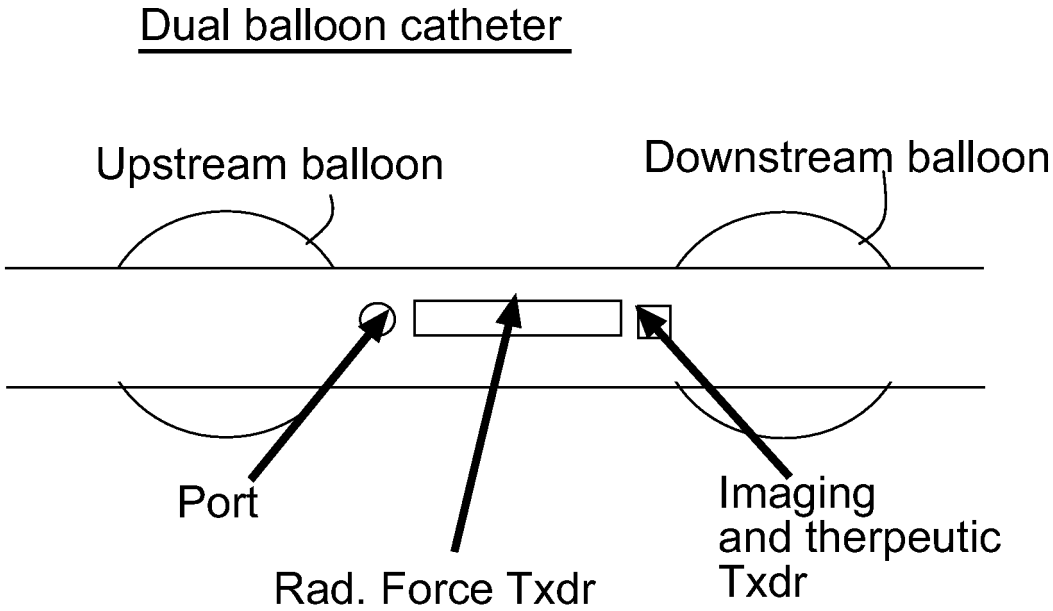


FIG. 14A



Balloon occluder upstream and downstream of bubble port and ultrasound transducer(s)

FIG. 14B

REFERENCES CITED IN THE DESCRIPTION

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专利名称(译)	使用超声能量和微泡的治疗和成像系统及其相关方法		
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申请号	EP2008841415	申请日	2008-10-24
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申请(专利权)人(译)	VIRGINIA专利大学基金会		
当前申请(专利权)人(译)	VIRGINIA专利大学基金会		
[标]发明人	HOSSACK JOHN A WAMHOFF BRIAN R KLIBANOV ALEXANDER L		
发明人	HOSSACK, JOHN, A. WAMHOFF, BRIAN, R. KLIBANOV, ALEXANDER, L.		
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摘要(译)

一种用于在受试者的一个或多个位置（例如脉管系统）处向治疗部位（例如狭窄或其他脉管系统疾病）提供治疗的方法和相关系统。该方法包括：将超声导管推进到受试者的治疗部位或靠近受试者的治疗部位;将微泡注入治疗部位或靠近治疗部位;并从超声导管输送超声能量。超声能量可以适于：对治疗部位成像，将微泡平移到治疗部位中或治疗部位附近和/或使微泡破裂。