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(54) **INTRAVASCULAR IMAGING DEVICE AND USES THEREOF**

INTRAVASKULÄRE BILDGEBENDE VORRICHTUNG UND IHRE VERWENDUNGEN  
DISPOSITIF D'IMAGERIE INTRAVASCULAIRE ET SES UTILISATIONS

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**Description****Technical Field**

5 [0001] The present invention is directed to a probe-type imaging device useful to visualize interior surfaces, e.g., the lumen of blood vessels. Specifically, the probe-type imaging device is useful for direct tissue imaging in the presence or absence of molecular imaging agents.

**Background**

10 [0002] Heart disease and stroke are the main cause of death in the United States. Most of the debilitating factors related to these diseases are rooted in vascular disorders. The main vascular insufficiencies are associated with vascular plaque formation and thrombus formation that block or decrease blood flow and, as a result, the oxygenated blood supply to these important organs. Medical device technologies and medication treatment are available to mechanically open  
15 the arteries or dilate them to avoid heart attack and stroke.

[0003] Percutaneous transluminal coronary angioplasty ("PTCA") was advanced by stents and medicated stents placement. Improvements of these methods are still required, however, to improve diagnosis and treatment of these diseases when they occur. Early detection and prevention of plaque and thrombus formation are needed to lower the incidence of first onset causing infarction and stroke; restenosis posttreatment and the efficacy follow-up of a therapy treatment.

20 [0004] Improvements of these methods are required to improve diagnosis and treatment of these diseases when they occur. Early detection and prevention of plaque and thrombus formation are still needed to lower the incidence of first onset causing infarction and stroke; restenosis post treatment and the efficacy follow-up of a therapy treatment.

[0005] There are a number of technologies currently in use for visualizing the lumen of vessels and diagnosing plaque, e.g., radiopharmaceuticals using PET and/or a beta probe, intravascular ultrasound (IVUS), intravascular MRI, intravascular IR, optical coherence tomography (OCT), intravascular temperature changes and their combinations. Different radionuclides are used in myocardial imaging of subjects at rest and after exercise for determining blood flow insufficiencies that indicate stenosis or measurements of other related physiological parameters. Ultrasound is used to image heart wall motion and to measure the blood ejection fraction. MRI imaging and Fast CT scanning are also used to measure similar physiological parameters that indicate stenosis. Direct measurement of plaque in the arteries uses high resolution CT imaging during a simultaneous intra-arterial injection of a contrast media that delineates the area of the narrowing of the artery during the catheterization procedure. OCT visualization of vessel involves the use of complicated and expensive instrumentation as well as the repeated saline washes to view the vessel wall.

[0006] In addition, CT, MRI and ultrasound imaging display spatial information differently from CCD light imaging. OCT disclose, in several patents, devices that are aimed at vessels and neoplastic tissue visualization. The utility of these devices is limited due to their complexity and use of mirrors, lens, and light focusing apparatuses required for light reflection propagation and visualization. Furthermore, the wall visualization requires blood washout using repeated saline flushes. Device positioning and registration require delicate and accurate guidewire 3 repositioning such as back and forth movements resulting in difficult therapy deployment.

[0007] Current imaging techniques using radiopharmaceuticals using PET and/or a beta probe, intravascular ultrasound (IVUS), intravascular MRI (IVMRI), intravascular IR, OCT, are not optimized. The current IVUS, IVMRI, intravascular IR, and intravascular thermal imaging techniques as well as the current scientific reports of in vivo molecular fluorescence tomography (MTF) (US 2004/0015062 A 1 and references therein) do not teach the use of a specific intra-tissue visualization device.

[0008] As such, there remains a need for a more inexpensive and sensitive and efficient devices for direct imaging of vessel lumen.

US 2003/0171691 A1 describes methods and devices for detecting vulnerable atherosclerotic plaque, or plaque at risk of reducing blood flow in a vessel, by identifying a region of elevated temperature along a living vessel wall. infrared heat-sensing catheters useful for identifying plaques in patients with disease of arteries are also described.

**Summary of the Invention**

[0009] The invention is as set out in claims 1 to 31.

[0010] In accordance with one embodiment of the present invention, a probe-type imaging device is provided that may be more sensitive than current methods of visualizing the vessel lumen and allows for more accurate diagnosis and improved deployments of stents or for the follow-up of therapy. The probe-type imaging device of the invention may also be useful in the early diagnosis of plaque formation, as well as in the identification of vulnerable plaque in individuals that are prone to developing it and/or patients undergoing catheterization.

[0011] In another embodiment, a catheter (or guidewire) probe-type imaging device is provided that can be useful for

clear visualization of the vascular system. The probe-type device may also be useful in non-medical applications, e.g., inspection in manufacturing facilities or sewer pipe. The probe-type imaging device of the invention, in one embodiment, provides for sensitive developed light technology detection (reflection and scatter), which can be useful for the visualization and inspection of any surface, e.g., metal, biological tissue, plastic or glass, and ceramic.

5 [0012] In another embodiment of the present invention, a method is provided using the probe-type imaging device for direct tissue imaging in the absence of a molecular imaging agent, e.g., contrast media. Alternatively, a method is provided using the probe-type imaging device for direct tissue imaging in combination with a molecular imaging agent (s). The use of molecular imaging agent for blood and/or tissue enhances tissue visualization. The method provided in connection with the present invention can reduce potential toxic effects of molecular imaging agents on a subject, as  
10 the concentrations required for contrast media using the probe-type imaging device of the invention are lower than the concentrations of contrast media required by existing imaging techniques. To that end, the probe-type imaging device of the invention may be useful for intra-tissue inspection.

15 [0013] In another embodiment, the probe-type imaging device of the invention utilizes photon detection enhancement as a function of changing the detected wavelength as compared to the emitted one. In doing so, the probe-type imaging device of the invention may be used to generate real-time tissue imaging, e.g., imaging and assessment of the vascular lumen, the cap and its thinning in vulnerable plaque. In addition, the probe-type device of the invention may be useful for precise stent deployment, when used alone, or in combination with other diagnostic modalities for drug delivery or, for instance, the delivery of a gene vector (e.g., viral vector) for gene therapy.

20 [0014] In another embodiment, the present invention provides a disposable imaging probe that is simple to use and that is relatively accurate. Unlike existing devices, the probe-type imaging device of the invention does not require the use of mirrors, lenses, or light focusing apparatuses for light reflection propagation and visualization.

25 [0015] In a further embodiment, the probe-type imaging device of the invention, unlike the other devices, such as that disclosed in US Patent No. 6,485,413 B1 and references cited therein, provides certain advantages, uses a multiple laser light source and does not require a focusing element. The direction and scope of the emitted light projected by the probe-type imaging device of the invention differs from other intravascular imaging devices, as light does not have to be redirected. The probe-type imaging device of the invention does not require the use of mirrors and simplifies concentration and cost. Specifically, the probe-type imaging device of the invention provides a detector array layout for efficient analysis of reflected and/or scattered light detection (the layout of detector allow detection of the vascular wall and its surroundings from different angles and views). In this manner, the probe-type imaging device can be applied to  
30 any catheter or guidewire 13.

35 [0016] In one embodiment, the probe-type imaging device of the invention may be provided with signal enhancement detection (using differential wavelength for emission and detection in combination with nanocrystal light manipulation). To this end, data acquisition and signal analysis and presentation may be implemented. Signal enhancement detection may further be implemented by using contrast media for specific enhancement of blood components for vessel lumen or vessel wall.

40 [0017] In another embodiment, the method of the present invention, unlike those currently available using MFT, such as those disclosed in US 6,081,322 and US 2004/0015062 A1 and references cited therein, do not focus on general *in vivo* imaging. Such imaging methods are limited, as potential non-accurate assessment of the image collection is due to light absorption and scatter evolved with depth (low resolution and sensitivity). Rather, the method of the present invention takes advantage of the absorption and scatter properties to provide a method for visualization of intravascular tissue and tissue border removal in neoplastic surgery, such as that associated with a subject undergoing surgery in the intestine or renal system.

45 [0018] In another embodiment, the device and methods of the invention may be used in combination with other detection methods such as thermal and beta probe. The probe-type imaging device of the invention may also be particularly useful in procedures that require shorter tissue depth inspection as the disclosed device is able to delineate minute abnormal tissue. In one embodiment, the probe-type imaging device of the invention may be used for a more localized therapy deployment, such as, stent, laser for plaque abolition or vascular wall stripping. Hydrostatic pressure, piezoelectric crystal, or other mechanical device may be useful to advance the probe-type imaging device detectors along a lumen, e.g., a vessel lumen.

50 [0019] The vascular vessel wall and their components including arteriosclerosis and vulnerable plaque have a limited depth of a few microns to a few millimeters and the use of light has several advantages for direct viewing and measure depth and thickness. In one embodiment, the probe-type imaging device is used to measure the time-of-flight from scattered light. In one embodiment, the probe-type imaging device of the invention may be useful in the measurement of time-of flight of scattered light where the light detectors have at least about from about 0.1 picoseconds to about 3  
55 picoseconds resolution.

[0020] The probe-type imaging device of the invention and methods of use thereof overcome the limitations of other known imaging methods by providing for: 1) a light and/or scatter measurement of the intravascular system; 2) variable wave length for testing; 3) real-time read of wall thickness; 4) real-time imaging of the vascular lumen system; 5) a probe

size that useful for stent or medication deployments; 6) increased sensitivity due to enhanced light and scatter; and 7) a 3D visualization of the vessel lumen.

[0021] The methods provided herein may be used to enhance the diagnosis and treatment of the tissue disorders, for example, a disorder of the cardiovascular system, such as, arteriosclerosis, atherosclerosis, or vessel aneurysm.

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### Brief Description of the Drawings

[0022] The invention will be further understood from the following description with reference to the figures, in which:

10 [0023] Figure 1 is a schematic diagram of one embodiment of a probe-type imaging device of the invention where a probe assembly is mounted on catheter end.

[0024] Figure 2 is a schematic diagram of one embodiment of a probe-type imaging device of the invention utilized to inspect a vessel wall.

[0025] Figure 3A is a schematic diagram of the ultraviolet region of the electromagnetic spectrum.

15 [0026] Figure 3B is a schematic diagram of the visible light region of the electromagnetic spectrum.

[0027] Figure 3C is a schematic diagram of the infrared region of the electromagnetic spectrum.

[0028] Figure 4A is a graph showing the relative scattered light intensity signal observed in normal vessel tissue and vessel plaque using a probe-type imaging device of the invention.

[0029] Figure 4B is a graph showing the relative time-of-flight of photons observed in normal vessel tissue and vessel plaque using a probe-type imaging device of the invention.

20 [0030] Figure 4C is a schematic diagram showing an image of normal vessel tissue and vessel plaque detected with a probe-type imaging device of the invention using near infrared or visible light.

[0031] Figure 4D is a graph showing the pattern of deviation of reflected light observed in normal vessel tissue, vessel plaque, and vulnerable vessel plaque using a probe-type imaging device of the invention.

[0032] Figure 5 is a cross-sectional view of the probe-type imaging device of the invention.

25 [0033] Figure 6 is a schematic diagram showing a probe-type imaging device in accordance with another embodiment of the invention. A cross-sectional view is shown at center. An oblique view of a fiber transmission bundle within a trunk region of the device is shown at left. Right side image shows oblique view of diodes/detectors in a detector assembly on the device. Illumination from central core used so generate optical signals and appears as triangles.

[0034] Figures 7 illustrates a schematic diagram of one embodiment of a probe-type imaging device of the invention utilized to inspect a vessel wall.

30 [0035] Figure 8A-B are a schematic diagram a probe-type imaging device utilized to inspect a vessel wall.

[0036] Figure 9 is a schematic diagram showing a probe-type imaging device in accordance with an embodiment of the invention.

[0037] Figure 10 is a schematic diagram showing one embodiment of a probe-type imaging device of the invention.

35 [0038] Figure 11 is a schematic diagram showing one embodiment of a probe-type imaging device of the invention.

[0039] Figure 12 is a schematic diagram showing one embodiment of a probe-type imaging device of the invention.

[0040] Figure 13 is a schematic diagram illustrating how time-of-flight is used to measure the time intervals (picoseconds) from pulsed light source from a disc shaped opening.

[0041] Figure 14 is a schematic diagram showing one embodiment of a probe-type imaging device of the invention.

40 [0042] Figure 15 is a schematic diagram showing one embodiment of a probe-type imaging device of the invention with a wrap-around photo-diode array and LED assembly.

[0043] Figure 16 is a schematic diagram showing one embodiment of a probe-type imaging device of the invention wherein wrap-around detector assemblies are fitted to catheter with staggered fit to produce a continuous spiral of detectors forming a 360 degree field of view.

45 [0044] Figure 17 illustrates an experimental probe setup. Drinking straw (Left) contains a double fiber optic probe held by a mechanical positioner. Rabbit aorta pinned to a flexible base placed on a microscope. A 10x objective was used to collect scattered light from delivery fiber (wavelengths>540 nm).

[0045] Figure 18 illustrates another experimental probe setup.

[0046] Figures 19 A-B illustrate vessel tissue obtained using a probe-type imaging device of the invention. Figure 19A, is a photograph showing a fiber-optic probe on the luminal surface of aortic tissue. Figure 19B, is a photograph showing an intensity graph micrograph of scattered light around a secondary vessel (darker region).

50 [0047] Figure 20A illustrates an experimental setup showing a probe-type imaging device of the invention being advanced down a vessel lumen.

[0048] Figure 20B illustrates light intensity micrographs obtained from a probe-type imaging device of the invention being advanced down a vessel lumen showing scattered light around a secondary vessel (darker region).

55 [0049] Figure 21A is an image of scattered light collected from a probe-type imaging device of the invention placed 245 microns above a tissue surface.

[0050] Figure 21B is a graph showing the intensity of scattered light collected from a probe-type imaging device of the

invention as a function of distance from a tissue surface.

[0051] Figure 21C is an image of scattered light collected from a probe-type imaging device of the invention placed near a tissue surface.

[0052] Figure 22A illustrates an intensity graph micrograph of scattered light around a secondary vessel (darker region).

[0053] Figure 22B illustrates a graph showing the relative scattered light intensity signal observed around a secondary vessel using the probe-type imaging device of the invention.

[0054] Figure 23 illustrates an experimental setup showing a probe-type imaging device of the invention being advanced down a vessel lumen.

[0055] Figure 24 is a schematic diagram showing a probe-type imaging device of the invention wherein illumination light delivered to tissue is carried in a single mode fiber with a central core of less than 9 microns used to deliver light to tissue.

[0056] Figure 25 is a schematic diagram of an experimental setup used to demonstrate scattered light imaging.

[0057] Figure 26A illustrates an intensity graph micrograph of scattered light from diseased rabbit aortic tissue as detected using a single mode fiber with a central core emitting light at 1024 nm wavelength.

[0058] Figure 26B illustrates showing an intensity graph micrograph of scattered light from normal rabbit aortic tissue as detected using a single mode fiber with a central core emitting light at 1024 nm wavelength.

[0059] Figure 26C illustrates an intensity graph micrograph of scattered light from diseased rabbit aortic tissue as detected using a single mode fiber with a central core emitting light at 532 nm wavelength.

[0060] Figure 26D illustrates an intensity graph micrograph of scattered light from normal rabbit aortic tissue as detected using a single mode fiber with a central core emitting light at 532 nm wavelength.

[0061] Figure 27 is a graph of the light intensity profile of diseased and normal tissue as determined using a single mode fiber with a central core emitting light at 532 nm or 1024 nm wavelength.

#### Detailed Description of Specific Embodiments

[0062] Referring now to Figure 1, there is shown a schematic diagram of a probe-type imaging device 10 in accordance with one embodiment of the invention. The device 10, in one embodiment, includes a probe assembly 11 mounted on one end of the imaging device 10. The probe assembly 11, in one embodiment, may be designed to emit radial illumination. As shown in Figure 1, the probe assembly 11 may include a body through which light may be transmitted along a guidewire 13, and on which photonic detectors may be affixed. The body 12 of the probe-type imaging device 10 can be any shape and dimension suitable for imaging within a vessel. In one embodiment, the body 12 of the probe-type imaging device 10 is shaped as a tube. The guidewire 13, useful in the probe-type imaging device 10 of the invention, can be of any type, size or dimension suitable for guiding the probe-type imaging device 10 of the invention. In one embodiment, the probe-type imaging device 10 of the invention has more than one photonic detector. The photonic detectors 14 can be affixed in any pattern suitable for the detection of emitted light. In one embodiment, the photonic detectors 14 may be connected to one another so that electrical signals can be received by each photonic detector and signals from each photonic detector can be received in an integrated fashion. The photonic detectors 14 can be of any size, shape, or dimension suitable for imaging. It should be noted that the probe-style imaging device 10 of the invention may be disposable.

[0063] An external cabinet (not shown) may be provided within which necessary optical, electrical and signal processing equipment (i.e., the receiving system) may be located along with a visual display (not shown) terminal freely positionable (i.e., remotely located) for optimal use in the procedure area. Light may be provided to the probe-style imaging device 10 of the invention from a light source. The light may be emitted from the probe-style imaging device 10 to illuminate a surface. In turn, emitted light contacts the surface and is then scattered and reflected back to a photonic detector on the probe-style imaging device 10. The photonic detector may be designed to convert the scattered and reflected light into an electrical signal. The electrical signal from the photonic detector may be transmitted to a receiving system, e.g., signal processing equipment (not shown), that converts the signal(s) into information using, for instance, a mathematical algorithm(s). The information resulting from the conversion of the photonic detector signal(s) can be displayed on a viewing screen as described below.

[0064] In one embodiment, the probe-type imaging device 10 may be useful for inspecting surfaces, e.g., a vessel wall. Figure 2 illustrates a schematic diagram of the probe-type imaging device 10 having multiple photonic detectors 14 utilized to inspect a vessel wall 22. As shown in Figure 2, a disk of light 21 illuminates the vessel wall 22. Signals from the multidetectors 14 may be displayed in real-time on a view screen used by the cardiologist. Real-time viewing of vessel features enables accurate and precise positioning and deployment of therapeutic interventions such as stents and phototherapy. Scattered light and reflected light from the vessel wall 22 may be picked up by the detectors 14. While the optical illumination assembly is not shown in Figure 2, single photon array detector 23 may measure time-of-flight of photons colliding with tissue features in plaque 24 (light colored speckled region) and in normal vessel wall 22 (solid gray colored region). In this manner, vessel dimensions and position of occlusions, partial blockages and vessel wall

22 protrusions can be revealed. Digital maps of the catheters position relative to anatomical landmarks can also be recorded and projected as 3-D vectors. Secondary measurements from back scattered photons 25 can give information of vessel wall 22 thickness. Diseased regions may be highlighted on the display screen and marked for more precise investigation. Light, diffusely scattered within tissue can reveal plaque location, plaque margins and plaque type. Light, directly reflected from vessel wall 22 surfaces can provide information about the physical characteristics of endothelial cells as well as cap composition of vulnerable plaques.

**[0065]** As shown in Figure 3A-C, the light that passes through the body of the probe-type imaging device 10 can be of any wavelength suitable for imaging. In one embodiment, the wavelength of light passing through the body of the probe-type imaging device 10 may be in the visible region of light (Figure 3A). The wavelength of light passing through the body of the probe-type imaging device 10 may also be in the ultraviolet region of light (Figure 3B), or the infrared region of light (Figure 3 C). The light may be visible light and/or near 1R light from CW diode or picosecond pulsed laser diodes. In one embodiment, a pulsed laser light source may be used in combination with single photon array detectors 23 (SPAD) of Fig. 2 affixed to the probe-type imaging device 10. This configuration may be particularly useful for detection in time-of-flight feature of the probe-type imaging device 10. In one embodiment, a time-correlated single photon counting (TCSPC) measurement setup may be used for analysis of photonic detector signals from the probe-type imaging device 10.

**[0066]** As detailed above, and further illustrated in Figures 4A-D, the probe-type imaging device 10 of the invention may be used to visualize tissue features, e.g., normal vessel tissue versus vascular plaque. As shown in Figure 4, signal from the probe 11 may be placed on view screen and recorded digitally. Figure 4A, illustrates a graph showing the relative scattered light intensity signal observed in normal vessel tissue and vessel plaque using the probe-type imaging device 10 of the invention. Figure 4B, illustrates a graph showing the relative time-of-flight of photons observed in normal vessel tissue and vessel plaque. Figure 4C, illustrates a schematic diagram showing an image of normal vessel tissue and vessel plaque detected with the probe-type imaging device 10 of the invention using near infrared or visible light. Figure 4D, illustrates a graph showing the pattern of deviation of reflected light observed in normal vessel tissue, vessel plaque, and vulnerable vessel plaque using the probe-type imaging device 10 of the invention.

**[0067]** Surface features of a vessel may be inspected and revealed by various detectors. Many different types of photonic detectors 23 can be affixed to the probe-type imaging device 10 of the invention, e.g., time-of-flight detectors, scattered light detectors, reflected light detectors. The probe-type imaging device 10 of the present invention may have a single type of photonic detector 23 affixed to the device 10, or a combination of different photonic detector 23 types affixed to the device 10. Any detector suitable for imaging may be useful with the probe-type imaging device 10 of the invention. As detailed below in Table 1, time-of-flight provides information on vessel dimensions and possible wall 22 protrusions into vessel lumen. Time-of-flight may be useful to give information relating to vessel wall 22 thickness in healthy tissue. Scattered light detectors 14, on the other hand, may be useful in revealing plaque location and type and plaque margins. Reflected light detector may be useful I in visualizing surface features of vessel wall 22, and to identify plaque type. Direct observation can be useful to guide the probe-type imaging device 10 of the invention. A vector-based 3-D projection of the vessel, as seen from an outside oblique orientation, gives anatomically accurate reference to vessel wall 22 features and highlights suspect areas and labels diseased regions.

Table 1  
Probe Features

Vessel Composition	Time-of-flight	Scattered Light	Reflected Light	Direct Observation
Normal	Reference	+	Reference	Reference
Plaque	+	++	++	+
Vulnerable Plaque	+	+++	+++	+

**[0068]** The probe-type imaging device 10 of the invention can be used for insertion into a lumen, i.e., the cardiovascular system, at medically standard access points (femoral artery, etc.). In one embodiment, the probe-type imaging device 10 of the invention may be designed for bodily insertion and adhere to the standard coatings and materials used in catheter construction. Catheters useful in the methods of the invention can be of any length, depending on the procedure involved. In one example, it can be about 3-6 feet in length.

**[0069]** The present invention, in an embodiment may provide a central, single mode coaxial fiber to deliver light to the distal end of the probe, as illustrated in Figure 5 and Figure 6. Figure 5 is a schematic diagram showing a cross-sectional view at a position along a section of the probe-type imaging device 50 of the invention. The diameter of the device 50, in an embodiment, may be about 2 French. A central coaxial or single mode fiber 51 delivers light to distal end and to detector assemblies (not shown). Three grooves act as channels 53A-C for optical fibers and wires 52 to/from the detector

assembly.

[0070] Figure 6 is a schematic diagram showing one embodiment of the probe-type imaging device 60 of the invention. A cross-sectional view of the probe-type imaging device 60 is shown at center. In one embodiment, the cross-sectional diameter of the probe-type imaging device 60 may be about 2 French or less. An oblique view of a fiber transmission bundle 61 is shown at left. In one embodiment, a small area detector 62 In/GaAs may be mounted either directly on the catheter and coupled to an optic fiber drawn parallel to the delivery fiber 61. In another embodiment of the invention, the small area detector In/GaAs may be remotely coupled to an optic fiber drawn parallel to the delivery fiber. Imaging can be performed either by bundling a large number of detectors 14/fibers along the device 10 or by rotating the device 10 with a single detector. The right side image in Figure 6 shows an oblique view of diodes/ detectors 63 in the detector assembly. Illumination from a central core may be used to generate optical signal and appears as, for instance, triangles. Three outer-grooves 64 in the device sheath 65 act as channels for fiber transmission bundle of optical fibers and wires to/from the detector assembly. The probe 60 may include features and components for stent deployment.

## DETECTION AND ANALYSIS FEATURES

### A. Scattered-light probe

[0071] In one embodiment, the probe-type imaging device of the invention may be a scattered-light-based probe 70. As illustrated in Figure 7, a point source such as circular gap 71 mode fiber can scatter light 73 to the tissue and may be detected by single or multiple photodetectors 72 embedded on catheter surface. Figure 8A, shows the low scattering of light observed from normal vessel tissue. Figure 8B, shows the high scattering of light from vessel plaque. As shown in Figure 7, and further illustrated in Figure 8A and 8B, a plaque B typically has a lower optical density, because it has more misaligned subcellular features and increased disorder than does normal vessel wall tissue A, and will give an increased diffuse light intensity relative to normal tissue. Light is scattered due to inelastic collisions between photons and tissue. Normal tissue, on the other hand, typically has a relatively well ordered structure with cells aligned along the vessel wall 22. Extracellular matrix exhibits well defined collective orientation. In plaque, the structure is chaotic with large amounts of extracellular material with poor orientation and cells with random orientation. Light scattering in those two situations is different, often with several orders of magnitude of change. In healthy tissue, small amounts of light will be scattered and the tissue will have a more transparent appearance. The diffuse scattering properties can be measured as the amount of backscattered light. Plaque scatters significantly larger amounts of light than does healthy tissue. Regions of diseased tissue may be identified by changes of light intensity and distance from the probe source.

[0072] Intensity of back-scattered light ( $I$ ) at various distances  $r$  from the point of entry of light, and the product of  $Ir^3$  is plotted semi logarithmically against  $r$ . The fractional change in optical mean free path ( $l$ ) can be determined from the following equation  $(d I / I = (1 + 2rs) - 1d F(r, I)$  as referenced in the paper: Miki H, Rogers RA, Lehr J, Butler JP. Geometric hysteresis in pulmonary surface-to-volume ratio tidal breathing. J Appl Physiol 1993; 75(4):1630-1636.

[0073] Near IR light may be used as the penetration depth for IR can be higher than for visible light, and the amount of backscattered may thus be lower. A high sensitivity detector, SPAD - avalanche photodiode, can be used to detect even small amounts of back-scattered light. Source and detector may be attached to a light frequency modulator. By making rapid adjustments in frequency, scattered light of various wavelengths can be detected. Furthermore, reflected light can be picked up and transmitted via the same assembly. In one embodiment, light diffusers may be used to deliver illumination light of appropriate frequency from the catheter to the vessel wall 22. Nanocrystals may also be embedded in the central core function as light diffusers. If embedded in the outer cladding of the catheter, physical properties of nanocrystals will be used as light amplifiers and specific wavelength detectors. Examples of light diffusers in the public domain are waveguide cavities, cracks in the fiber and coaxial coating, and mirrors.

[0074] In one embodiment, the light emitted from the probe-type device of the invention may be emitted from an angled feature to the surrounding surface, *e.g.*, tissue. In another embodiment, the light emitted from the probe-type device of the invention may be emitted from a the fiber end to the surrounding surface, *e.g.*, tissue. As illustrated in Figure 9, in one embodiment, the light emitted from the present probe-type imaging device 90 may be emitted from a circular gap 91 to the surrounding surface, *e.g.*, tissue. Source and detector 92 may be attached to a light frequency outside the device 90. By making rapid adjustments in frequency, scattered light of various wavelengths can be detected. Furthermore, reflected light can be picked up and transmitted *via* the same assembly. In one embodiment, nanocrystals embedded in central core 93 function as light diffusers and re-direct light toward vessel wall to give spherical illumination. Inspection tool can be tuned to detect scattered or reflected light and to specifically detect emission spectra from exogenously applied fluorescent dyes.

[0075] In one embodiment, the probe-type imaging device can integrate therein detector arrays 94 in flexible sheets, offset and wrapped around the length of the device, with each sheet 94 containing multiple photodiode detectors in a packed array 95 organized as diagonal, strip, cross, ring or other configuration. Each photodiode 95 may be bounded with LED strips for illumination. Diodes 95 can be photon counting and intensity sensing.

**B. Reflected-light probe**

[0076] In one embodiment, the probe-type imaging device of the invention can be a reflected-light-based probe 100 as illustrated in Figure 10. A reflected-light probe 100 of the invention may be used to provide information about plaque and plaque cap covering vulnerable plaque. As shown in Figure 10, during operation, a photon stream 10 may be released from a point source, and after striking a tissue surface 102, may be reflected back 104 to detector(s) 103. Signal intensity may be generated from the number of photons counted. Light reflected from normal tissue will have a significantly different reflected light signal from tissue within a plaque.

[0077] As illustrated in Figure 11, in one embodiment, the light source and detector on probe-type imaging device 110 may be coupled to a light frequency modulator (not shown). This configuration can be used to make rapid adjustments in frequency, so that light of various wavelengths can be detected by the probe-type imaging device 110 of the invention. Furthermore, reflected-light can be picked up and transmitted *via* the same assembly. In an embodiment, nanocrystals 111 may be embedded in outer cladding 112 function to act as specific wavelength detectors. Inspection tool can be tuned to detect scattered, reflected and to specifically detect emission spectra from exogenously applied fluorescent dyes or other compounds bound to specific structures on and within vessel walls.

**C. Time-of-Flight probe**

[0078] In one embodiment, the probe-type imaging device of the invention may be design as a time-of-flight probe 120 as illustrated in Figure 12. In this configuration, the probe-type imaging device 120 can be used to measure time-of-flight of scattered light where light detectors 121 have at least about 3 picoseconds resolution. In another embodiment, the probe-type imaging device 120 can be designed to measure time-of Hight of scattered light where the sight detectors 121 have at least about 0.1 picoseconds resolution.

[0079] In this case, single photons may be released from a point source 122 and the time-of-flight before the photon is re-detected may be measured. Photons traveling through, for instance, thick tissue 123 will take more time (picoseconds). Time-of flight measurements may be used to determine the total distance a photon travels before reaching a detector. The distribution of traveling times for a large number of photons can reveal information about the scattering properties of the material. In weakly scattering materials, detected photons have a low probability of inelastic collisions and the majority of backscattered photons have only collided once, resulting in a single narrow distribution of travel times. In highly scattering materials, the detected backscattered photons have a wider distribution of travel times, as the may undergo multiple collisions, resulting in a wide spread of travel distances and times. The average travel distance can, however, be shorter in highly scattering materials due to a higher probability for collision. This calls for an analysis of the distribution of travel times, and in certain tissues (plaque), the experiment can be tuned into giving multimodal distributions of travel times that can be analyzed as multiscatter evens compared to a single modal distribution for weakly scattering materials (healthy tissue).

[0080] Figure 13 illustrates a schematic diagram of how time-of-flight may be used to measure the time intervals (picoseconds) from pulsed light source from a disc shaped opening. A detector array 130 may be arranged to pick up first entry of photons for each point detector 13 1. Many (in this example, 50) detectors 131 can be arranged in the detector array 130, or arranged in multiple grooves 132, *e.g.*, 3 to 4 grooves. The intensity of each detector 131 can generate a pixel map, as the device is moved down the vessel lumen. Time-of-flight gives the shape, while scattered and reflected light can reveal the nature and distribution of the plaque.

**D. Optical imaging probe**

[0081] In one embodiment, the probe-type imaging device of the invention may be used as an optical imaging probe 140, as illustrated in Figure 14. In such an embodiment, the optical imaging probe 140, may have a diameter of at least about 0.5 mm, and may be about 1 mm to about 2 mm. The central coaxial (not shown) fiber of the optical image probe 140 in one embodiment, may have a circumference of at least about 3 mm, and may be from about 5 mm to about 7 mm. In one embodiment, more than about 40 photon detectors 141 may be affixed to the surface of the optical imaging probe 140. The pattern for which the array of detectors 141 may be arranged can similar to that illustrated in Figure 14 or circumferentially about the probe, *e.g.*, in a ring or wrap-around pattern, such as that shown in Figures 15 and 16. The ring pattern can be a series of rings on the surface of the optical imaging probe 140. In one embodiment, a light source 142 may be proximal to detector array 141 on optical imaging probe 140 and may be provided with multiple wavelengths. The detector array 141, in an embodiment, can be designed so that it rotates to enable optical imaging of local environment, while the light source 142 and catheter may remain stationary or rotate to enable optical imaging of the local environment. Visual information may be encoded and can be presented in real-time. A 3-D vector diagram of the vessel wall may be projected for plaque mapping and is useful as a reference.

[0082] In accordance with one embodiment, the light source 142 may be provided with a wrap-around photo diode

array and LED assembly 151 as shown in Figure 15. The diodes array 151 can be placed in any pattern suitable for imaging (e.g., a diagonal, strip, cross, or other geometric pattern). In one embodiment of the invention, integrators and signal processors 153 may be alternated in the wrap-around photo diode array, with electrical leads 154 overlapping and interconnecting adjacent assemblies. Wrap-around detector assemblies 160, as shown in Figure 16, can be positioned in a staggered pattern on the device 150 to produce a continuous spiral of detectors forming a 360 degree field-of view as illustrated in Figure 16. In this manner, the detector assembly 160 can be advanced forward as the device 150 is rotated. The rotation and advancement mechanism may be mechanical, hydraulic, crystalline or electronic means, e.g., piezo crystal. Alternatively, the detector assembly 160 may remain stationary.

## FLUORESCENCE AND CONTRAST MEDIA

**[0083]** Molecular imaging in one embodiment, combines molecular agents with imaging tools to capture pictures of specific molecular pathways in the body, particularly those that are key targets in disease processes. Molecular imaging holds a unique potential of simultaneously being able to find, diagnose and treat disease *in vivo*, as well as the ability to depict how well a particular treatment is working. The probe-style imaging device of the present invention, in an embodiment, may be used in molecular imaging techniques. The invention provides methods for molecular imaging using the probe-style device of the invention in combination with molecular imaging agents, e.g., fluorescence and contrast media.

**[0084]** In accordance with an embodiment, the probe-type imaging device 10, such as that illustrated in Fig. 1 of the invention may be used in the examination of structural and compositional features innate to the vessel, and may be used with exogenously applied or delivered probes of chemical, fluorescent, molecular, ionizing or radioactive origin. The probe-type imaging device of the invention can be tuned to detect scattered, reflected and to specifically detect emission spectra from exogenously applied fluorescent dyes.

**[0085]** Fluorescence and chemoluminescence chromophores and light excitation in the following wavelength can routinely be used both *in vitro* and *ex vivo* for diagnosis to delineate cells, cell tracking, cell components and molecular structures and other imaging related research investigation. Photodynamic therapy and near infrared fluorescent *in vivo* imaging received special interest in recent years. Many recent reports claim improved imaging methods in the infrared fluorescence and using new chemical preparations. *In vivo* imaging using these techniques initiated the design of new imaging devices such as, Molecular Fluorescence Tomography.

**[0086]** At present, without significant technology improvements, most if not all the proposed fluorescence imaging have limited use. A few factors determine their adoption and their widespread use as a beneficial diagnostic imaging modality in the clinic. One factor contributing to the utility of a fluorescent imaging modality may be the nature of the fluorescent compound and its activation wavelength. The targeting and adequate concentration in the diseased tissue as compared to its environment (target to non target ratio) contributes to the utility of a fluorescent imaging modality. The type of excitation light and its in-depth penetration that allows for 2D or 3D image collections, as well as the properties of the imaging device (sensitivity and resolution as a function of depth) can limit the utility of a fluorescent imaging modality.

**[0087]** More difficult factors are associated with the nature of the specific disease and/or the physiological parameter to be measured. *In vivo* situation of administered molecular probes, such as contrast agents, in conjunction with current imaging technologies may be limited due to the following:

- Potential toxicity due the necessary large concentration of fluorescence contrast media required to delineate specific tissue.
- The mechanism for trapping and washout has to be identified prior to its acceptance (in vivo stability, metabolite identification).
- The characteristics of the specific binding and pharmacokinetics of the fluorescence agent.
- Similar obstacles were encountered in developing MRI contrast agents that have longer *in vivo* half-life in tissue.

**[0088]** The probe-type imaging device of the invention may also be useful in functional imaging methods such as, blood flow measurements, increased concentration in tumor, increased accumulation in areas of brain where there is a breakdown in BBB.

**[0089]** The use of the probe-type imaging device of the present invention in combination with imaging agents can be advantageous when utilizing infrared excitation light for non-toxic chromophores. Specifically, such a combination can allow for the detection of the spectral signature of diseased tissue due to the fluorescence and thereafter calibrate and quantify the fluorescence spectral signature of diseased tissue.

**[0090]** Unique fluorescence labeled molecules like proteins, DNA and other bioactive molecules and compounds have been effectively utilized in both *in vitro* and *ex vivo* investigations. However, most of the proposed agents, methods and teaching of MFT have limited *in vivo* application in human imaging due to one or several of the above mentioned reasons. Therefore, more specific agents and uses are needed.

[0091] In accordance with one embodiment, the probe-type imaging device of the present invention can be used for *in vivo* light (e.g., fluorescence) imaging, including: 1) a specific area of imaging and/or specific fluorescent contrast media; 2) a visualization and light inspection of the intravascular device; and to select agents and methods that extend the use of light imaging to other internal organs and to MFT.

[0092] In another embodiment of the invention, the probe-type imaging device of the invention may be useful for optical intravascular visualization. The probe-type imaging device can provide light images of the intravascular lumen and walls using a variety of wavelength for emission and for several wavelengths for detection. The probe-type imaging device may also be useful where the wavelengths for light emission and detection are not the same. In such a scenario, the probe-type imaging device can provide light images in combination with a fluorescence contrast media. The probe-type imaging device of the invention may also be useful in the visualization and image analysis of lumen opening (vertical view) and wall thickness (horizontal view) displayed in real-time on the imaging and signal display screen. The probe-type imaging device of the invention may further be useful in CCD light imaging *via* reflection or scatter detection.

[0093] In another embodiment, the probe-type imaging device of the present invention can be used in combination with vascular contrast agents with *in vivo* pharmacokinetics suited for concentrating in blood or vessel wall components. Vascular contrast agents that concentrate in vascular wall components can be useful in revealing inflammation, infection, calcification, smooth muscle proliferation and/or fatty tissue accumulation as part of the plaque formation process. The probe-type imaging device of the invention may, therefore, be useful in the diagnosis of inflammation, infection, calcification, smooth muscle proliferation and/or fatty tissue accumulation as part of the plaque formation process in a subject. The probe-type imaging device of the present invention can also be used with agents designed to enhance imaging, providing fluorescence image contrast as compared to the normal vasculature, to provide diagnostic visualization of, for instance lesions, infection, plaque, thrombus cell tracking and therapy deployment in the vascular system.

[0094] Agents that use a combination detection system of positron or gamma emission on one hand and fluorescence or chemo luminescence on the other hand can take advantage of the vast knowledge developed by both technologies.

## Contrast Media

[0095] Molecular imaging agents that can be used with the probe-type imaging device of the invention are similar to those described in US patents Nos. 6,592,847 B1 ; 2003/0044353 A1 ; 2004/0015062 A1 ; 6,511,967 B1 ; 2003/017017 A1 ; 6,319,488 B1 , 6,403,625 B1 ; 6,630,570 B1 and references therein; as well as US 6,630,570 B1, US 6,319,488; and MFT 6,592,847 B1; 2003/0044353 A1; 2004/0015062 A1; 6,511,967 B1; 2003/017017 A1.

[0096] MFT agents may be constructed of three basic parts as follows:

- Chromophores probe (e.g., a near infrared dye);
- Targeting moiety (e.g., DNA, proteins, peptides); and
- Delivery molecule (e.g., polymeric backbone).

[0097] MFT agents useful in imaging methods with the probe-type imaging device of the present invention can be from about 2 Kd to about 1000 Kd in size. These agents, preferably, can target specific *in vivo* molecular constructs, such as, light quenched probes, enzyme activity and gene expression at the targeted sites.

[0098] The methods disclosed in connection with the present invention provide protocols that may be more tissue-specific than current methods using MFT. In one embodiment, the probe-type imaging device of the invention may be used to visualize tissue with a thickness of a few microns to a few millimeters in a vessel or neoplastic tissue, as compared to several centimeters required for organ visualization in human. The invention also provides imaging methods useful to target specific cellular components of the vessel cell wall. The probe-type imaging device of the invention is not limited to the use of near infrared dyes. Agents that are constructed of the chromophores and activated chromophores (<2KD), and chromophores that are directly attached to a targeting molecule (<2KD), may also be useful in visualization methods utilizing the probe-type imaging device of the present invention. In certain embodiments of the invention, the molecular weight of the agents used may be smaller than 2 Kd in size. In some embodiments of the invention, molecules that are constructed of the fluorescent and/or other contrast media attached to the polymeric molecule, but without a targeting entity, may be used in combination with the probe-type imaging device of the invention. In these cases the polymeric molecule is the targeting entity and the molecular weight may be over 2KD (no polymeric backbone). In another embodiment the probe-type imaging device of the invention may be used in combination with light emitting agents labeled with a radionuclide to allow for dual imaging detection.

[0099] Imaging agents and contrast agents particularly useful in the imaging methods of the present invention are as follows:

[0100] 1. Contrast media with the following potential structure: pharmacophores directly label blood components

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such as hemoglobin, red cells, platelets and are preincubated with blood or blood components or injected directly into a mammal; chemically activated chromophores which when contact with blood components results in a relatively stable chemical bond. The nature of this covalent bond is an interaction of the following (Table 2)

- i. Free amino groups in blood proteins with a chromophores activated aster
- ii. Free -SH groups in blood proteins with a chromophore activated aster
- iii. Exposed carboxylic groups in blood with a chromophore activated amino
- iv. Blood proteins with complex with metal chromophores complexes
- v. Blood components with targeted activated chromophores
- vi. Other blood conjugate for imaging blood components (Table 2a)

Table 2. Activated fluorescent dyes for direct *in vivo* labeling by IV injection

Compound	Components Labeled
Chromophore-Anhydride	Blood
Chromophore-Acylchloride	Blood
Chromophore-N-hydroxysuccinamide	Blood
Chromophore-Activated esters	Blood
Chromophore-Isothiocyanate	Blood
Chromophore-Melamide	Blood

Table 2a :Fluorescent conjugates for blood imaging

Compound	Components Labeled
Albumin-chromophore isothiocyanate	Blood components
polylysine -chromophore isothiocyanate	Blood components
chromophore- IgG	Blood components + Infection
Phalloidin-Fluorescein isothiocyanate	Blood components
Lectin-Fluorescein isothiocyanate	BC + glycoproteins cancer+ Infection

**[0101]** 2. Free molecular chromophores (unattached) that have affinity to a specific tissue due to the physical, chemical or structural properties. Examples include lipophilic cationic dyes (rhodamine 123, S 13, dequilibrium, porphyrins)(which may not have been used specifically for imaging) and others (see list). Due to their lipophilicity and dispersed positive charge, they can concentrate preferably in certain tumor cells. Breast carcinoma cells for example, poses an enhanced negative charge on their membrane, the mitochondria has a negative charge that is stronger by 3 to 4 orders of magnitude, therefore, these dyes will concentrate preferably in these tumors. These agents have specific light activation and fluorescence properties that could be used with a specific light detector, as it would be appreciated from the description of the device. (Table 3).

Table 3: Chromophores for direct tissue visualization n

Fluorescent dye	MW	Indication
Mag-Indo-1 N,N'-bis(salicylidene)	594.7	Mg <sup>2+</sup>
Ethylenediamine	268.3	Mg <sup>2+</sup>
Potassium-binding benzofuran isophthalate-AM	1171	K <sup>+</sup> mitochondria
6-Methoxy-1-(3-sulfopropyl) quinolinium monohydrate	281	chloride by quenching; Measurement of membrane chloride transport
9,9'-Bis(N-methylacridinium nitrate)	510	superoxide

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(continued)

Fluorescent dye	MW	Indication
Tris (4,7-diphenyl-1,10-phenanthroline) ruthenium(II) dichloride complex	1169	oxygen probe blood and skin
Quinones	<2KD	melanoma and cancer
Rhodamine-based	<2KD	cancer carcinoma
Porphyrin-based		cancer infection, inflammation
Dequalinium	<2KD	cancer mitochondria
S13		cancer mitochondria
Tetraalkyl phosphonium based	<2KD	blood flow
Amino acid color reaction reagent (DNP)	<2KD	blood
Chromophore = any old or novel chromophores. A chromophore as used herein means functional groups with characteristic optical absorptions or the molecules which contain them.		

**[0102]** 3. Chromophores that are bound directly or via a short tether to specific molecules that have enhanced function in the tissue of interest. *I.e.*, chromophores attached to metabolites (fatty acids in heart, specific sugar and amino acid in tissue), ligands (with specific receptor function, hormone, alpha and beta blockers) or antibody (antigen antibody interaction). Antisense-vector-chromophore to delineate the over-expression or under-expression of gene(s) in a specific tissue. The agents proposed do not contain a polymeric construct for delivery as described in (US 6,592,847 B1; 2003/0044353 A1; 2004/0015062 A1; 6,511,967 B1; 2003/017017 A1. (Table 4)

Table 4: Chromophores directly attached to metabolites, receptor ligands, and specific abnormal cell penetration vectors

Agent combination	Example	Use
Metabolite--chromophore	omega-phenantrene-pentadecanoic acid	Heart
Hormone - chromophore	triphenyl-16-estradiol-phosphonium Nitrate	breast
Apoptotic agent - chromophore	A (6-8) amino acid truncated derivative of Annexin-V - Cyanine dye	Apoptosis
Blood flow agent - Chromophore	4-chromophor-triphenyl phosphonium nitrate	Heart
Storage agent - chromophore	Aryl-guanidine - Chromophore	Brain and adrenal tumors
Prostate binder-chromophore Acetylcholine - chromophores	chain alkyl amine-chromophores	Prostate

**[0103]** 4. For visualization with the disclosed device, the preferred agents may be plaque and plaque formation targeting molecules that can be directly attached to a fluorescent tag by a chemical bond, a tether or a complex (Table 5).

Table 5: Chromophores with short tether specific attachment

Agent combination	Example	Use
Biotin(vector)-agent-chromophore	Biotin-antisense-chromophore	Prostate
Biotin-chromophore	Biotin-chromophore	Infection
Adenosine-chromophore	Adenosine-tether-Cyanine dye	Heart
Ap4A analog-chromophore	Ap2(Chromophore)p2A	Plaque
Acetylcholine receptor agonist/antagonist	RS 86 -chromophore	Alzheimer's Disease

**[0104]** The following agents may also be useful in the imaging methods provided in the present invention:

1. MRI contrast media that concentrate in plaque vascular components will have different scatter and reflected light and could be used, for example Gd and Fe targeted compounds, complexes, liposome, miscelles.

2. CT contrast agents like iodinated or polyiodinated plaque targeted agents will have different scattered and reflected light therefore can be appropriate for imaging. Toxicity is less of a problem than MRI.

3. Fluorescence and chemoluminescence agents (Tables 2-4).

**[0105]** These agents may be particularly useful when the light viewing with the probe-type imaging device is used in combination with other imaging modalities.

## References

**[0106]**

MicroLens for detector : Wu MH, Paul KE, Whitesides GM. 2002. Patterning flood illumination with microlens arrays. Appl. Opt. May 1 ;41 (13):2575-85. Single photon emitter as light source: Gudiksen MS, Lauhon LJ, Wang j, Smith DC, Lieber CM. 2002. Growth of nanowire superlattice structures for nanoscale photonics and electronics. Nature. Feb 7;415(6872): 617-20.

Diffuse light scattering for theory: Butler JM, Miki H, Squarcia S, Rogers RA, Lehr JL. 1996. Effect of macroscopic deformation on lung microstructure. J. Appl. Physiol. 81 (4): 1792-99.

## Examples

**[0107]** It will be expressly understood that the examples provided hereinafter are merely representative of the possible embodiments of the invention, and that these examples are the illustrative of the far greater range of formats which are potentially possible and useful within the invention.

### Example 1 Imaging of Rabbit Aorta

**[0108]** A working scattered-light prototype of the probe-type imaging device was demonstrated using excised pieces of rabbit aorta and a modified confocal microscope. Figure 17 illustrates an experimental probe setup. The drinking straw 170 (left) contained a double fiber optic probe 171 held by a mechanical positioner 172. Rabbit aorta 173 was pinned to a flexible base 174 placed on a microscope 175. A 10x objective was used to collect scattered light from delivery fiber 171 (wavelengths>540 nm). Although crude in construction (drinking straw, double fiber optic probe held by a mechanical positioner) the device records measurable differences in diffusely scattered light collected by a 10x objective at wavelengths greater than 510 nm. As shown in Figure 18 light was delivered to the luminal surface of aorta 173. Scattered light was detected 10's of microns away from probe tip.

**[0109]** Figures 19A-B, illustrate visualization of vessel tissue obtained by placing the probe-type imaging device 190 on the vessel luminal surface 191. Figure 19A illustrates a fiber-optic probe 190 on the luminal surface of aortic tissue 191. Figure 19B illustrates an intensity graph micrograph of scattered light around a secondary vessel, e.g., lumen 192 (darker region). As shown in Figures 19 A-B, scattered light diffusely escaping from tissue revealed a detectable and measurable signal. Lumens 192 from secondary vessels remain dark and distinguishable.

**[0110]** Figures 20A-B illustrate visualization of vessel tissue obtained by advancing the probe-type imaging device along a vessel luminal surface. Figure 20A, illustrates an experimental setup showing a probe-type imaging device 200 of the invention being advanced down a vessel lumen 201. Figure 20B shows in series light intensity micrographs obtained from a probe-type imaging device 200 of the invention being advanced down a vessel lumen showing scattered light around a secondary vessel 202 (darker region). Scattered light detection showed alterations of vessel wall features the probe is advanced along the vessel luminal surface.

**[0111]** As shown in Figures 21 A-C, a signal obtained from the probe-type imaging device was not sensitive to probe proximity to vessel wall surface. Figure 21A, is an image of scattered light collected from a probe-type imaging device of the invention placed 245 microns above a tissue surface. Figure 21B, is a graph showing the intensity of scattered light collected from a probe-type imaging device as a function of distance from a tissue surface. Figure 21C, is an image of scattered light collected from a probe-type imaging device of the invention placed near a tissue surface. As detailed in Figures 21A-C, the light signal detected from vessel wall was insensitive to illumination source above vessel wall

surface.

[0112] As detailed above and further illustrated in Figures 22A-B, features in the vessel wall were detected in scattered light detection mode. Variations in light intensity tracked with physical changes in vessel wall. Figure 22A, illustrates an intensity micrograph of scattered light around a secondary vessel 221 (darker region). Figure 22B, is a graph showing the relative scattered light intensity signal observed around a secondary vessel using the probe-type imaging device of the invention.

[0113] Figure 23 illustrates an experimental setup showing a probe-type imaging device 230 of the invention being advanced down a vessel lumen 231. Diffuse scattered light was derived from the detection of the mean free optical path of photons escaping from tissue.

## Example 2 Imaging of Diseased and Normal Rabbit Aorta Tissue Regions

[0114] Light intensities detected from diseased and normal regions of rabbit aorta were examined using light from 488 nm fluorescent light, 532 nm and 1024 nm light from a solid state diode source as illustrated in Figure 24. Shown in Figure 24 illumination light was delivered to tissue via a single mode fiber 240 with a central core 241 of less than about 9 microns. A photodiode 242 placed near the fiber tip collected scattered and reflected light from the tissue.

[0115] Figure 25 is a schematic diagram of an experimental setup used to demonstrate scattered light imaging. A diseased experimental piece of aorta 250 was placed on microscope stage. A fiber optic imaging probe 251 was placed parallel, or at an oblique angle to the lumen surface. Light from a diode laser (not shown) passing through the fiber 251 illuminated a local region at the fiber end. Multiple photodetectors 252 placed above the fiber end detected the light (same frequency) scattered from the surrounding tissue 253. Diseased tissue 250 was identified by changes of light intensity and distance from the probe 251 tip. Intensity of back scattered light ( $\lambda$ ) at various distances  $r$  from the point of entry of light, and the product of  $Ir^3$  was plotted semi logarithmically against  $r$ . The fractional change in optical mean free path ( $\lambda$ ) were determined from the following equation ( $\delta \lambda/\lambda = (1 + 2rs) \cdot -1 \delta F(r, \lambda)$ ) as referenced in the paper: Miki H, Rogers RA, Lehr J, Butler JP. Geometric hysteresis in pulmonary surface-to-volume ratio tidal breathing. J Appl Physiol 1993; 75(4):1630-1636.

[0116] Detection spectra observed from diseased and normal regions of rabbit aorta are shown in Figure 26A-D. Figure 26A, is a photograph showing an intensity graph micrograph of scattered light from diseased rabbit aortic tissue as detected using a probe-type imaging device emitting light at 1024 nm wavelength. Figure 26B, is a photograph showing an intensity graph micrograph of scattered light from normal rabbit aortic tissue as detected using a probe-type imaging device emitting light at 1024 nm wavelength. Figure 26C, is a photograph showing an intensity graph micrograph of scattered light from diseased rabbit aortic tissue as detected using a probe-type imaging device emitting light at 532 nm wavelength. Figure 26D, is a photograph showing an intensity graph micrograph of scattered light from normal rabbit aortic tissue as detected using a probe-type imaging device emitting light at 532 nm wavelength. Light from both the 532 nm light source and the 1024 nm light source exhibited a higher mean intensity in diseased tissue than light scattered from normal tissue. Regions of interest were indicated and pixel intensities were plotted on the graph shown in Figure 27. Figure 27 is a graph of the light intensity profile of diseased and normal tissue as determined using one embodiment of a probe-type imaging device. The graphical representation on the pixel intensities as a function of the region of interest confirmed that the light from both the 532 nm light source and the 1024 nm light source exhibited a higher mean intensity in diseased tissue than light scattered from normal tissue.

## Equivalents

[0117] Although particular embodiments have been disclosed herein in detail, this has been done by way of example for purposes of illustration only, and is not intended to be limiting with respect to the scope of the appended claims which follow. For instance, the selection of the photonic detector pattern and type as well as the imaging agent is considered within the skill of the ordinary artisan.

## Claims

1. An intravascular imaging device [10] comprising:

a probe [11] having a body portion [12];

a passageway in the body portion [12] through which a guide wire [13] can be extended for guiding movement of the probe;

a light source [21] on the body portion [12] of the probe for directed emission of light to a tissue surface; and  
characterised by

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a detector array [14] positioned on the body portion [12] proximal to the light source [21] for detecting light scattered and reflected from the tissue surface, so that image signals from the detected light can be generated for display in real time.

- 5     **2.** An imaging device [10] as set forth in claim 1, wherein the light source [21] can generate light along a spectrum of wavelengths.
- 3.** An imaging device [10] as set forth in claim 1, wherein light from the light source [21] can include one of visible light, ultraviolet light, infrared light, and pulsed laser light.
- 10     **4.** An imaging device [10] as set forth in claim 1, wherein the detector array [14] is positioned on the body portion [12] of the probe [11] such that scattered and reflected light can be detected from various angles for subsequent imaging of the surrounding intravascular area.
- 15     **5.** An imaging device [10] as set forth in claim 1, wherein the detector array [14] includes one of a scattered light detector [72], a reflected light detector [103], a time-of-flight detector [121], or a combination thereof.
- 6.** An imaging device [10, 150] as set forth in claim 1, wherein the detector array [160] is arranged circumferentially about the body portion [12] of the probe to enable a 360 degree field of view of surrounding tissue.
- 20     **7.** An imaging device [10, 150] as set forth in claim 1, wherein the detector array [160] is capable of rotating about the body portion to enable a 360 degree field of view of surrounding tissue.
- 8.** An imaging device [10] as set forth in claim 1, wherein the light source [21] and the detector array [14] are integrated into one assembly.
- 25     **9.** An imaging device [10] as set forth in claim 8, wherein the assembly is arranged circumferentially about the body portion [12] of the probe to enable a 360 degree field of view of surrounding tissue.
- 30     **10.** An imaging device [10] as set forth in claim 8, wherein the assembly is capable of rotating about the body portion [12] to enable a 360 degree field of view of surrounding tissue.
- 11.** An imaging device [10] as set forth in claim 8, wherein the assembly includes a plurality of alternating light source and detectors.
- 35     **12.** An imaging device [10] as set forth in claim 8, wherein the assembly further includes at least one signal processor and at least one integrator.
- 13.** An imaging device [10] as set forth in claim 1, further including a light frequency modulator in communication with the light source [21] for relatively rapid adjustment of the frequency of light emitted.
- 40     **14.** An imaging device [10] as set forth in claim 1, further including a light diffuser [93] for light emitted to surrounding tissue.
- 15.** An imaging device [10] as set forth in claim 1, further including a light amplifier for light emitted to surrounding tissue.
- 45     **16.** A method for imaging using an imaging device as claimed in any one of claims 1 to 15, the device adjacent to a tissue surface to be imaged, the method comprising:
  - 50           activating the device for directed emission of light to the tissue surface;
  - detecting light scattered and reflected from the tissue surface while detector assembly remains stationary; and
  - generating, in real time, an image of the tissue surface from the detected light for display.
- 17.** A method as set forth in claim 16, wherein in the step of activating, directed emission includes one of emission of light in a circular pattern, emission at an angle from the probe, and emission from an end of the probe to the tissue surface.
- 55     **18.** A method as set forth in claim 16, further including displaying, in real time, on a monitor the generated image for viewing of the tissue surface.

19. A method according to claim 16, wherein the tissue surface to be imaged has been targeted with a medium of a contrasting agent.
- 5 20. A method as set forth in claim 19, wherein the medium of a contrasting agent includes pharmacophores capable of labeling a blood component including hemoglobin, red blood cells, and platelets.
- 10 21. A method as set forth in claim 20, wherein the contrasting agent includes one of chromophore-anhydride, chromophore-acylchloride, chromophore-Nhydroxysuccinamide, chromophore-activated esters, chromophore-isothiocyanate, chromophore-melamide, albumin-chromophore isothiocyanate, polylysine- chromophore isothiocyanate, chromophore-IgG, pallocidin-fluorescein isothiocyanate, and lectinfluorescein isothiocyanate.
- 15 22. A method as set forth in claim 19, wherein the medium of a contrasting agent includes free molecular pharmacophores having affinity to a specific tissue through one of physical, chemical, or structural properties.
- 20 23. A method as set forth in claim 22, wherein the contrasting agent includes one of lipophilic cationic dyes, mag-indo-1N,N'-bis(salicylidene), ethylenediamine, potassiumbinding benzofuran isophthalate-AM, 6-methoxy- 1-(3-sulfopropyl) quinolinium monohydrate, 9,9'-bis(N-methylacridinium nitrate), tris(4,7-dipheyl-I, 10- phenanthrolin) ruthenium (II) dichloride complex, quinones, rhodamine-based, porphering-based, dequelinium, S I3, tetraphenyl phosphonium-based, and amino acid color reaction reagent (DNP).
- 25 24. A method as set forth in claim 19, wherein the medium of a contrasting agent includes pharmacophores attached to one of metabolites, receptor ligands, and specific abnormal cell penetration vectors.
- 25 25. A method as set forth in claim 24, wherein the contrasting agent includes one of metabolite-chromophore, hormone-chromophore, aseptotic agent-chromophore, blood flow agent-chromophore, storage agent-chromophore, prostate binder-chromophore, and acetylcholine-chromophore.
- 30 26. A method as set forth in claim 19, wherein the medium of a contrasting agent includes pharmacophores with a short tatter to specific molecules having enhanced function in tissue of interest.
- 30 27. A method as set forth in claim 26, wherein the contrasting agent includes one of biotin( vector )-agent -chromophore, biotin-chromophore, adenosine-chromophore, ap4analog-chromophore, and acetylcholine receptor agonist/antagonist.
- 35 28. A method as set forth in claim 19 wherein the medium of a contrasting agent includes one of an MRI contrast medium that concentrates in plaque vascular components, a CT conrasing agent that target plaques, and a flourescence and chemoluminescence agent.
- 40 29. A method as set forth in claim 19, wherein the step of activating includes providing a light frequency modulator for relatively rapid adjustment of the frequency of light emitted to the surrounding tissue.
- 40 30. A method as set forth in claim 19, wherein the step of activating includes providing a light diffuser for light emitted to the surrounding tissue.
- 45 31. A method as set forth in claim 19, wherein the step of activating includes providing a light amplifier for light emitted to the surrounding tissue.

## Patentansprüche

- 50 1. Intravaskuläre Abbildungsvorrichtung (10), enthaltend:
- eine Sonde (11) mit einem Körperabschnitt (12);
- einen Kanal im Körperabschnitt (12), durch welchen ein Führungsdraht (13) zur Führung der Bewegung der
- 55 Sonde geführt werden kann;
- eine Lichtquelle (21) an dem Körperabschnitt (12) der Sonde für die direkte Bestrahlung einer Gewebeoberfläche mit Licht; und **gekennzeichnet durch**
- eine Detektoranordnung (14), die in dem Körperabschnitt (12) proximal zu der Lichtquelle (21) angeordnet ist,

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um von der Gewebeoberfläche gestreutes und reflektiertes Licht zu erfassen, so dass von dem erfassten Licht Bildsignale zur Anzeige in Echtzeit erzeugt werden können.

- 5 2. Abbildungsvorrichtung (10) nach Anspruch 1, bei welcher die Lichtquelle (21) Licht über ein Spektrum von Wellenlängen erzeugen kann.
3. Abbildungsvorrichtung (10) nach Anspruch 1, bei welcher Licht von der Lichtquelle (21) entweder sichtbares Licht, ultraviolettes Licht, Infrarotlicht oder gepulstes Laserlicht einschließen kann.
- 10 4. Abbildungsvorrichtung (10) nach Anspruch 1, bei welcher die Detektoranordnung (14) an dem Körperabschnitt (12) der Sonde (11) dergestalt angeordnet ist, dass gestreutes und reflektiertes Licht aus verschiedenen Winkeln für die anschließende Abbildung des umgebenden intravaskulären Bereichs erfasst werden kann.
- 15 5. Abbildungsvorrichtung (10) nach Anspruch 1, bei welcher die Detektoranordnung (14) entweder einen Detektor (72) für gestreutes Licht, einen Detektor (103) für reflektiertes Licht, einen Flugzeitdetektor (121) oder eine Kombination daraus enthält.
- 20 6. Abbildungsvorrichtung (10, 150) nach Anspruch 1, bei welcher die Detektoranordnung (160) um den Körperabschnitt (12) der Sonde über den Umfang angeordnet ist, um ein 360°-Sichtfeld des umgebenden Gewebes zu ermöglichen.
7. Abbildungsvorrichtung (10, 150) nach Anspruch 1, bei welcher die Detektoranordnung (160) in der Lage ist, um den Körperabschnitt zu rotieren, um ein 360°-Sichtfeld des umgebenden Gewebes zu ermöglichen.
- 25 8. Abbildungsvorrichtung (10) nach Anspruch 1, bei welcher die Lichtquelle (21) und die Detektoranordnung (14) in einer Baugruppe integriert sind.
9. Abbildungsvorrichtung (10) nach Anspruch 8, bei welcher die Baugruppe um den Körperabschnitt (12) der Sonde über den Umfang angeordnet ist, um ein 360°-Sichtfeld des umgebenden Gewebes zu ermöglichen.
- 30 10. Abbildungsvorrichtung (10) nach Anspruch 8, bei welcher die Baugruppe in der Lage ist, um den Körperabschnitt (12) zu rotieren, um ein 360°-Sichtfeld des umgebenden Gewebes zu ermöglichen.
- 35 11. Abbildungsvorrichtung (10) nach Anspruch 8, bei welcher die Baugruppe eine Vielzahl von Lichtquellen und Detektoren abwechselnd aufweist.
12. Abbildungsvorrichtung (10) nach Anspruch 8, bei welcher die Baugruppe ferner mindestens einen Signalprozessor und mindestens einen Integrierer enthält.
- 40 13. Abbildungsvorrichtung (10) nach Anspruch 1, ferner enthaltend einen Lichtfrequenzmodulator in Kommunikation mit der Lichtquelle (21) für die relativ rasche Einstellung der Frequenz des emittierten Lichts.
14. Abbildungsvorrichtung (10) nach Anspruch 1, ferner enthaltend einen Lichtdiffusor (93) für das auf das umgebende Gewebe emittierte Licht.
- 45 15. Abbildungsvorrichtung (10) nach Anspruch 1, ferner enthaltend einen Lichtverstärker für das auf das umgebende Gewebe emittierte Licht.
- 50 16. Abbildungsverfahren unter Verwendung einer Abbildungsvorrichtung nach einem der Ansprüche 1 bis 15, welche Vorrichtung einer abzubildenden Gewebeoberfläche benachbart ist, welches Verfahren enthält:  
Aktivierung der Vorrichtung für die gerichtete Emission von Licht auf die Gewebeoberfläche;  
Erfassen des von der Gewebeoberfläche gestreuten und reflektierten Lichts, während die Detektoranordnung stationär bleibt; und  
Erzeugen einer Abbildung der Gewebeoberfläche aus dem erfassten Licht zur Anzeige in Echtzeit.
- 55 17. Verfahren nach Anspruch 16, bei welchem in dem Schritt der Aktivierung die gerichtete Emission entweder die Emission von Licht in einem kreisförmigen Muster, die Emission in einem Winkel von der Sonde oder die Emission von einem Ende der Sonde auf die Gewebeoberfläche einschließt.

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18. Verfahren nach Anspruch 16, ferner enthaltend die Anzeige des erzeugten Bildes in Echtzeit zur Betrachtung der Gewebeerfläche auf einem Monitor.
- 5 19. Verfahren nach Anspruch 16, bei welchem die abzubildende Gewebeerfläche mit einem Kontrastmittelmedium behandelt wurde.
20. Verfahren nach Anspruch 19, bei welchem das Kontrastmittelmedium Pharmakophore enthält, die in der Lage sind, einen Blutbestandteil einschließlich Hämoglobin, roten Blutzellen und Plättchen zu markieren.
- 10 21. Verfahren nach Anspruch 20, bei welchem das Kontrastmittel einen Stoff aus Chromophor-Anhydrid, Chromophor-Acylchlorid, Chromophor-N-Hydroxysuccinamid, Chromophor-aktivierten Estern, Chromophor-Isothiocyanat, Chromophor-Melamid, Albumin-Chromophor-Isothiocyanat, Polylysin-Chromophor-Isothiocyanat, Chromophor-IgG, Palloldin-Fluorescein-Isothiocyanat und Lectinfluorescein-Isothiocyanat enthält.
- 15 22. Verfahren nach Anspruch 19, bei welchem das Kontrastmittelmedium freie molekulare Pharmakophore enthält, die durch eine von physikalischen, chemischen oder strukturellen Eigenschaften eine Affinität für ein spezifisches Gewebe haben.
- 20 23. Verfahren nach Anspruch 22, bei welchem das Kontrastmittel einen Stoff aus lipophilen kationischen Farbstoffen, Mag-indo-1N,N'-bis(salicyliden), Ethylendiamin, Kalium-bindendem Benzofuran-Isophthalat-AM, 6-Methoxy-1-(3-sulfopropyl)-chinolinmonohydrat, 9,9'-Bis(N-methylacridinnitrat), Tris(4,7-dipheyl-1,10-phenanthrolin)-Ruthenium (II)-dichloridkomplex, Chinonen, Rhodamin-basiertem, Porpherin-basiertem, Dequelinium-, S I3, Tetraphenylphosphonium-basiertem und Aminosäure-Farbreaktionsreagens (DNP) enthält.
- 25 24. Verfahren nach Anspruch 19, bei welchem das Kontrastmittelmedium Pharmakophore enthält, die an einen Stoff aus Metaboliten, Rezeptorliganden und spezifischen abnormalen Zellpenetrationsvektoren gebunden sind.
- 30 25. Verfahren nach Anspruch 24, bei welchem das Kontrastmittel einen Stoff aus Metaboliten-Chromophor, Hormon-Chromophor, aseptotischem Wirkstoff-Chromophor, Blutflusswirkstoff-Chromophor, Speicherwirkstoff-Chromophor, Prostatabinder-Chromophor und Acetylcholin-Chromophor enthält.
- 35 26. Verfahren nach Anspruch 19, bei welchem das Kontrastmittelmedium Pharmakophore mit einem "short tatter" zu spezifischen Molekülen enthält, die eine gesteigerte Funktion in dem Gewebe von Interesse haben.
- 40 27. Verfahren nach Anspruch 26, bei welchem das Kontrastmittel einen Stoff aus Biotin-(vektor)-Wirkstoff-Chromophor, Biotin-Chromophor, Adenosin-Chromophor, ap4-Analog-Chromophor und Acetylcholinrezeptor-Agonist/Antagonist enthält.
- 45 28. Verfahren nach Anspruch 19, bei welchem das Kontrastmittelmedium eines aus einem MRI-Kontrastmedium, welches sich in vaskulären Plaque-Komponenten konzentriert, einem CT-Kontrastmittel, welches Plaques zum Ziel hat, und einem Fluoreszenz- und Chemolumineszenz-Wirkstoff enthält.
- 50 29. Verfahren nach Anspruch 19, bei welchem der Schritt der Aktivierung die Bereitstellung eines Lichtfrequenzmodulators für die relativ rasche Einstellung der Frequenz des auf das umgebende Gewebe emittierten Lichts einschließt.
30. Verfahren nach Anspruch 19, bei welchem der Schritt der Aktivierung die Bereitstellung eines Lichtdiffusors für das auf das umgebende Gewebe emittierte Licht einschließt.
31. Verfahren nach Anspruch 19, bei welchem der Schritt der Aktivierung die Bereitstellung eines Lichtverstärkers für das auf das umgebende Gewebe emittierte Licht einschließt.

### Revendications

- 55 1. Dispositif d'imagerie intravasculaire [10] comprenant :
- une sonde [11] ayant une portion de corps [12] ;  
un passage dans la portion de corps [12] à travers lequel un fil métallique de guidage [13] peut être étendu

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pour guider le mouvement de la sonde ;

une source de lumière [21] sur la portion de corps [12] de la sonde pour une émission dirigée de lumière sur une surface de tissu ; et **caractérisé par** :

un réseau de détecteurs [14] disposé sur la portion de corps [12], proximal par rapport à la source de lumière [21], pour détecter la lumière diffusée et réfléchie par la surface de tissu de sorte que les signaux d'image provenant de la lumière détectée puissent être générés pour un affichage en temps réel.

2. Dispositif d'imagerie [10] selon la revendication 1, dans lequel la source de lumière [21] peut générer de la lumière sur un spectre de longueurs d'onde.

3. Dispositif d'imagerie [10] selon la revendication 1, dans lequel la lumière provenant de la source de lumière [21] peut comprendre de la lumière choisie entre de la lumière visible, de la lumière ultraviolette, de la lumière infrarouge ou de la lumière de laser pulsée.

4. Dispositif d'imagerie [10] selon la revendication 1, dans lequel le réseau de détecteurs [14] est positionné sur la portion de corps [12] de la sonde [11] de sorte que la lumière diffusée et réfléchie puisse être détectée sous divers angles pour une imagerie ultérieure de la zone intravasculaire environnante.

5. Dispositif d'imagerie [10] selon la revendication 1, dans lequel le réseau de détecteurs [14] comprend un détecteur choisi parmi un détecteur de lumière diffusée [72], un détecteur de lumière réfléchie [103], un détecteur de temps de vol [121] ou une combinaison de ceux-ci.

6. Dispositif d'imagerie [10, 150] selon la revendication 1, dans lequel le réseau de détecteurs [160] est aménagé circonférentiellement autour de la portion de corps [12] de la sonde pour permettre un champ de vision de 360 degrés du tissu environnant.

7. Dispositif d'imagerie [10, 150] selon la revendication 1, dans lequel le réseau de détecteurs [160] est capable de tourner autour de la portion de corps pour permettre un champ de vision de 360 degrés du tissu environnant.

8. Dispositif d'imagerie [10] selon la revendication 1, dans lequel la source de lumière [21] et le réseau de détecteurs [14] sont intégrés en un seul ensemble.

9. Dispositif d'imagerie [10] selon la revendication 8, dans lequel l'ensemble est aménagé circonférentiellement autour de la portion de corps [12] de la sonde pour permettre un champ de vision de 360 degrés du tissu environnant.

10. Dispositif d'imagerie [10] selon la revendication 8, dans lequel l'ensemble est capable de tourner autour de la portion de corps [12] pour permettre un champ de vision de 360 degrés du tissu environnant.

11. Dispositif d'imagerie [10] selon la revendication 8, dans lequel l'ensemble comprend une pluralité de sources de lumière et de détecteurs alternants.

12. Dispositif d'imagerie [10] selon la revendication 8, dans lequel l'ensemble comprend en outre au moins un processeur de signal et au moins un intégrateur.

13. Dispositif d'imagerie [10] selon la revendication 1, comprenant en outre un modulateur de fréquence de lumière en communication avec la source de lumière [21] pour un ajustement relativement rapide de la fréquence de la lumière émise.

14. Dispositif d'imagerie [10] selon la revendication 1, comprenant en outre un diffuseur de lumière [93] pour la lumière émise sur le tissu environnant.

15. Dispositif d'imagerie [10] selon la revendication 1, comprenant en outre un amplificateur de lumière pour la lumière émise sur le tissu environnant.

16. Procédé d'imagerie utilisant un dispositif d'imagerie selon l'une quelconque des revendications 1 à 15, le dispositif étant adjacent à une surface de tissu à imager, le procédé comprenant les étapes consistant à :

activer le dispositif pour une émission dirigée de lumière sur la surface de tissu ;

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détecter la lumière diffusée et réfléchiée par la surface du tissu tandis que l'ensemble de détecteurs reste stationnaire ; et  
générer en temps réel une image de la surface du tissu à partir de la lumière détectée pour affichage.

- 5 17. Procédé selon la revendication 16, dans lequel, à l'étape d'activation, l'émission dirigée comprend une émission de lumière choisie parmi une émission de lumière selon un motif circulaire, une émission sous un certain angle par rapport à la sonde et une émission d'une extrémité de la sonde à la surface du tissu.
- 10 18. Procédé selon la revendication 16, comprenant en outre l'affichage en temps réel sur un moniteur de l'image générée pour observer la surface du tissu.
19. Procédé selon la revendication 16, dans lequel la surface du tissu à imager a été ciblée avec un milieu d'un agent de contraste.
- 15 20. Procédé selon la revendication 19, dans lequel le milieu d'agent de contraste comprend des pharmacophores capables de marquer un composant sanguin, notamment l'hémoglobine, les globules rouges et les plaquettes.
- 20 21. Procédé selon la revendication 20, dans lequel l'agent de contraste comprend l'un des suivants : chromophore-anhydride, chromophore-chlorure d'acyle, chromophore-N-hydroxysuccinamide, esters activés aux chromophores, chromophore-isothiocyanate, chromophore-mélamide, albumine-chromophore isothiocyanate, polylysine-chromophore isothiocyanate, chromophore-IgG, palloïdine-fluorescéine isothiocyanate et lectine-fluorescéine isothiocyanate.
- 25 22. Procédé selon la revendication 19, dans lequel le milieu d'agent de contraste comprend des pharmacophores moléculaires libres ayant une affinité avec un tissu spécifique via l'une des propriétés physiques, chimiques ou structurelles.
- 30 23. Procédé selon la revendication 22, dans lequel l'agent de contraste comprend l'un des suivants : colorants cationiques lipophiles, mag-indo-1N,N'-bis(salicylidène), éthylènediamine, isophtalate-AM de benzofuranne se liant au potassium, monohydrate de 6-méthoxy-1-(3-sulfopropyl)quinolinium, 9,9'-bis(nitrate de N-méthylacridinium), complexe de dichlorure de tris(4,7-diphényl-1,10-phénanthroline)ruthénium(II), quinones, réactifs réagissant à la couleur (DNP) à base de rhodamine, de porphyrine, de déquélium, de S 13, de tétraphénylphosphonium et d'acides aminés.
- 35 24. Procédé selon la revendication 19, dans lequel le milieu d'agent de contraste comprend des pharmacophores fixés à des métabolites, à des ligands récepteurs ou à des vecteurs de pénétration spécifiques de cellules anormales.
- 40 25. Procédé selon la revendication 24, dans lequel l'agent de contraste comprend l'un des suivants : métabolite-chromophore, hormone-chromophore, agent azeptotique-chromophore, agent d'écoulement sanguin-chromophore, agent de stockage-chromophore, liant de prostate-chromophore et acétylcholine-chromophore.
- 45 26. Procédé selon la revendication 19, dans lequel le milieu d'agent de contraste comprend des pharmacophores avec un court fragment de molécules spécifiques ayant une fonction améliorée dans des tissus d'intérêt.
- 50 27. Procédé selon la revendication 26, dans lequel l'agent de contraste comprend l'un des ensembles suivants : agent (vecteur) de biotine-chromophore, biotine-chromophore, adénosine-chromophore, analogue d'ap4-chromophore et agoniste/antagoniste de récepteur d'acétylcholine.
- 55 28. Procédé selon la revendication 19, dans lequel le milieu d'agent de contraste comprend un milieu choisi entre un milieu de contraste MRI qui se concentre dans des composants vasculaires de plaques, un agent de contraste CT qui cible des plaques et un agent de fluorescence ou de chimioluminescence.
29. Procédé selon la revendication 19, dans lequel l'étape d'activation comprend la fourniture d'un modulateur de fréquence de lumière pour un ajustement relativement rapide de la fréquence de la lumière émise sur le tissu environnant.
30. Procédé selon la revendication 19, dans lequel l'étape d'activation comprend la fourniture d'un diffuseur de lumière pour la lumière émise sur le tissu environnant.

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**31.** Procédé selon la revendication 19, dans lequel l'étape d'activation comprend la fourniture d'un amplificateur de lumière pour la lumière émise sur le tissu environnant.

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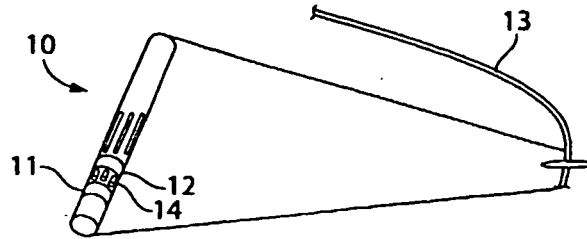
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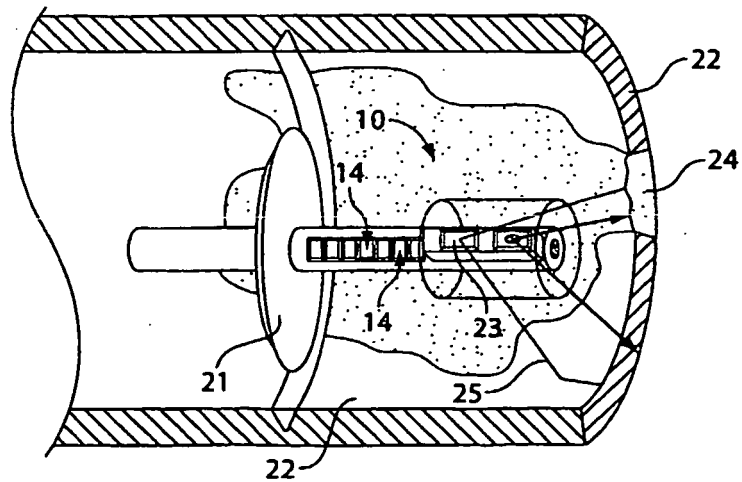
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**INSPECTION CATHETER AND STENT DELIVERY  
DEVICE UTILIZING INTRA-VITAL IMAGING  
OF BLOOD VESSEL CONSTITUENTS**



**Fig. 1**

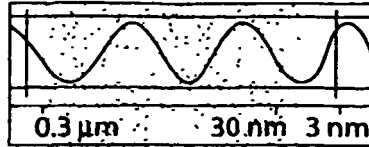
**MULTIPLE DETECTORS**



**Fig. 2**

ULTRAVIOLET WAVES

**ULTRAVIOLET REGION  
OF THE ELECTROMAGNETIC SPECTRUM**

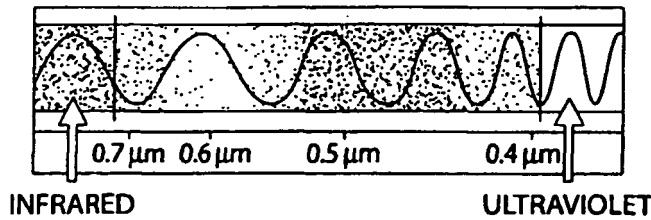


NEAR UV    FAR UV    EXTREME UV

**Fig. 3A**

VISIBLE LIGHT WAVES

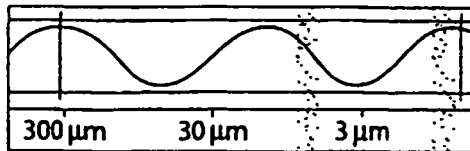
**VISIBLE LIGHT REGION  
OF THE ELECTROMAGNETIC SPECTRUM**



**Fig. 3B**

THE INFRARED

**INFRARED REGION OF THE  
ELECTROMAGNETIC SPECTRUM**



FAR    MID    NEAR

**Fig. 3C**

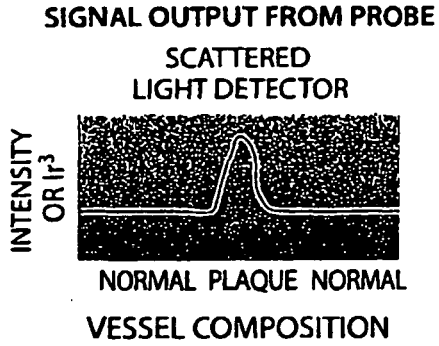


Fig. 4A

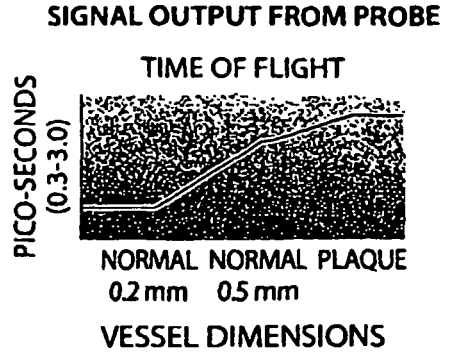


Fig. 4B

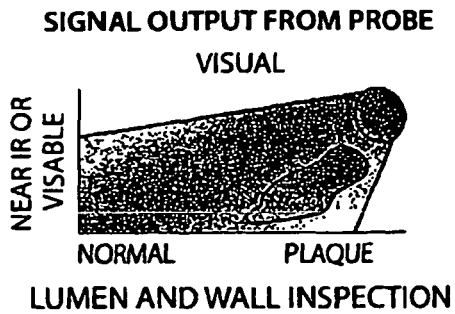


Fig. 4C

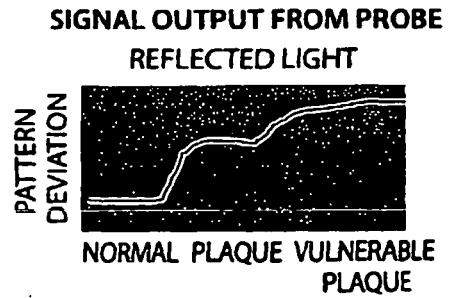


Fig. 4D

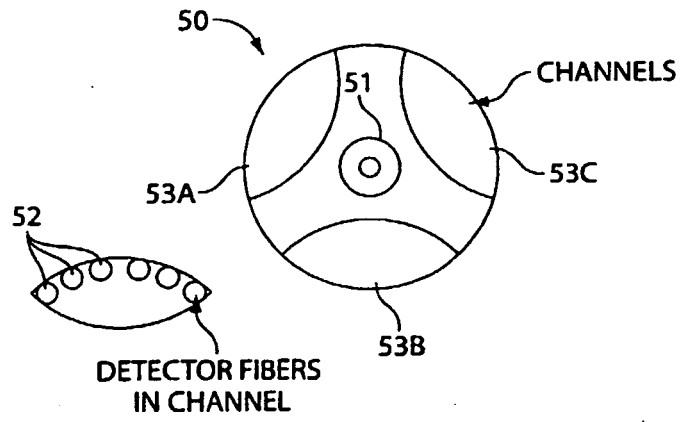


Fig. 5

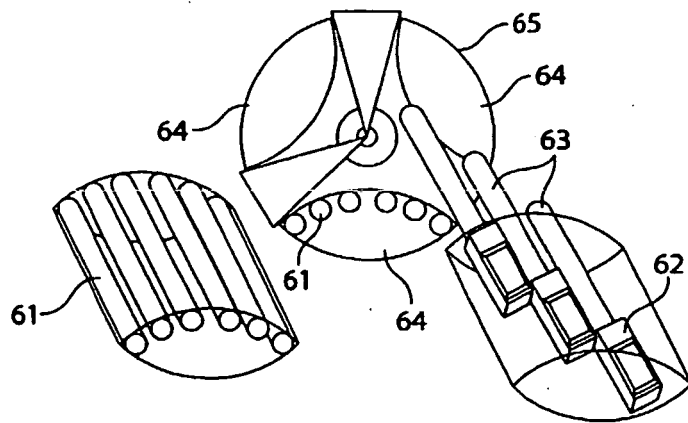
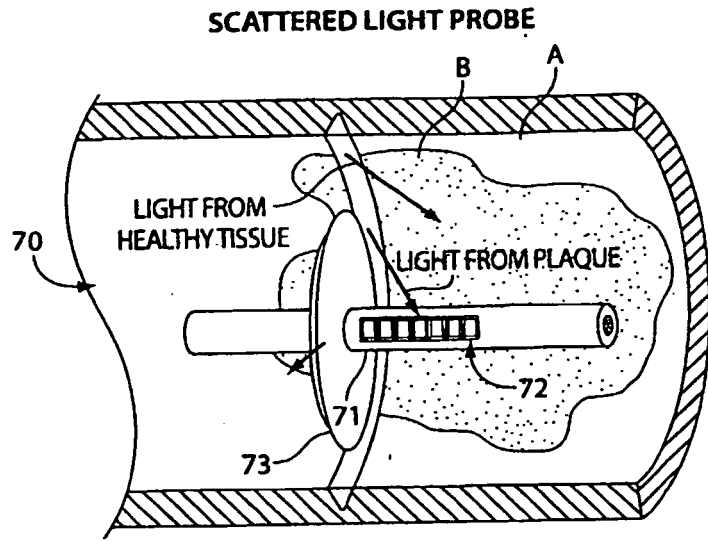
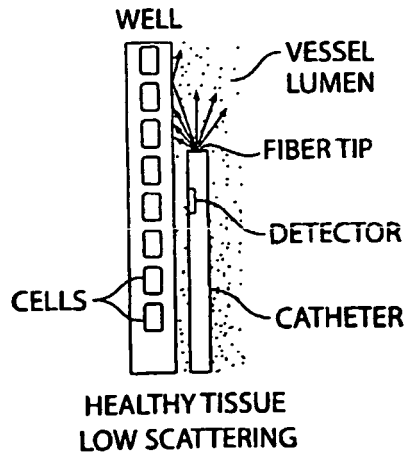


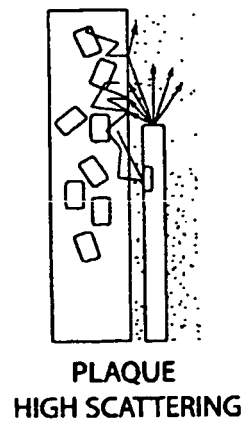
Fig. 6



**Fig. 7**

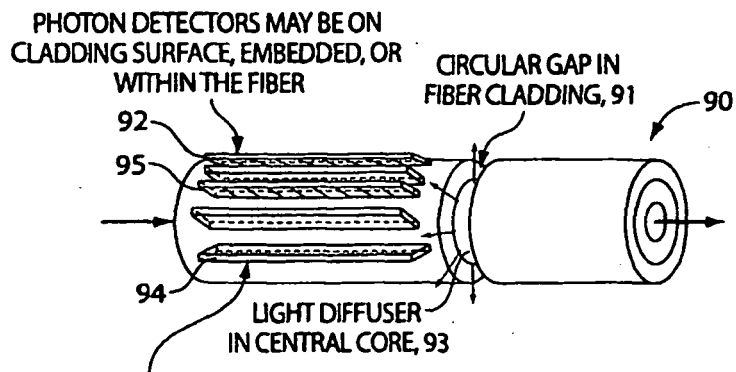


**Fig. 8A**



**Fig. 8B**

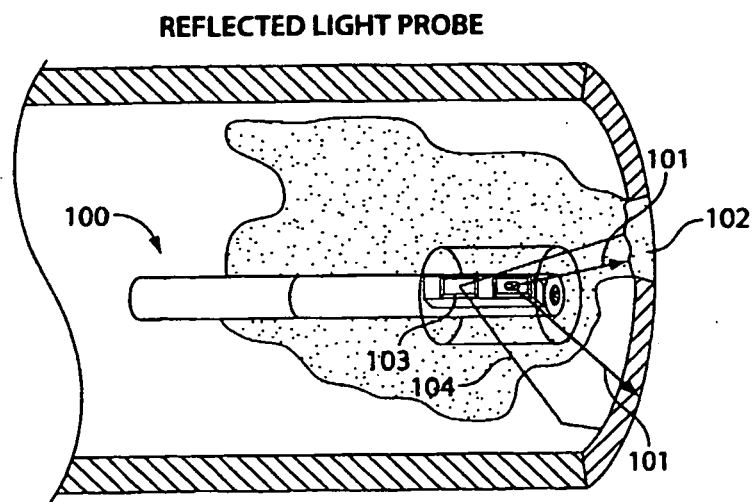
**SCATTERED LIGHT DETECTOR FOR  
FIBER-COUPLED INSPECTION DEVICE**



NARROW, LINEAR SLITS IN COATING  
PERMIT SCATTERED LIGHT ENTRY FROM  
TISSUE INTO PHOTON DETECTOR ARRAY

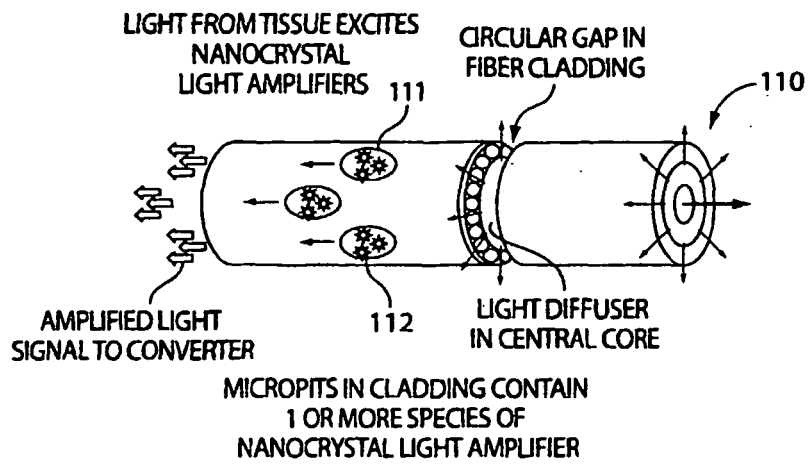
COAXIAL OR MULTIMODE FIBER: CENTRAL CORE CARRIES VISIBLE, NearIR LIGHT  
FROM SOURCE OUTSIDE THE DEVICE, OUTER CORE CARRIES SCATTERED LIGHT FROM  
PROBE TIP TO CONVERTER OUTSIDE INSPECTION TOOL, OR TO THE PHOTON DETECTORS  
LOCALLY MOUNTED AT THE SLITS, FIBER CLADDING IS IMPERMANENT TO LIGHT  
EXCEPT FOR SLITS, HOLES AND GAPS DESIGNED INTO PROBE.

**Fig. 9**



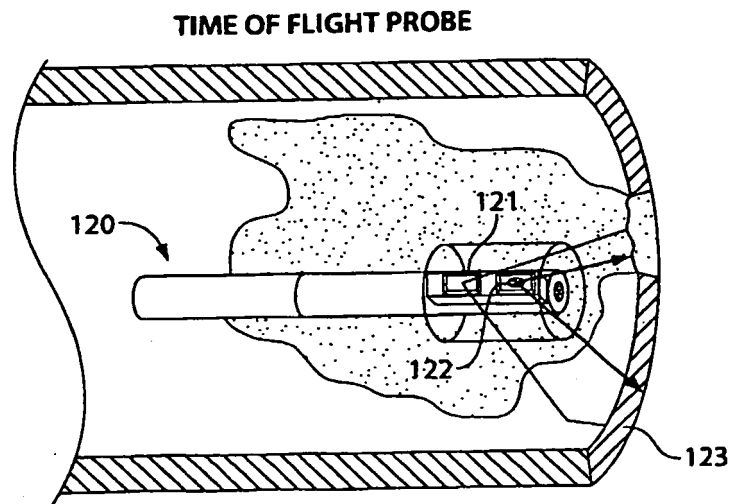
**Fig. 10**

**REFLECTED/FLUORESCENT LIGHT DETECTOR  
FOR FIBER-COUPLED INSPECTION DEVICE**

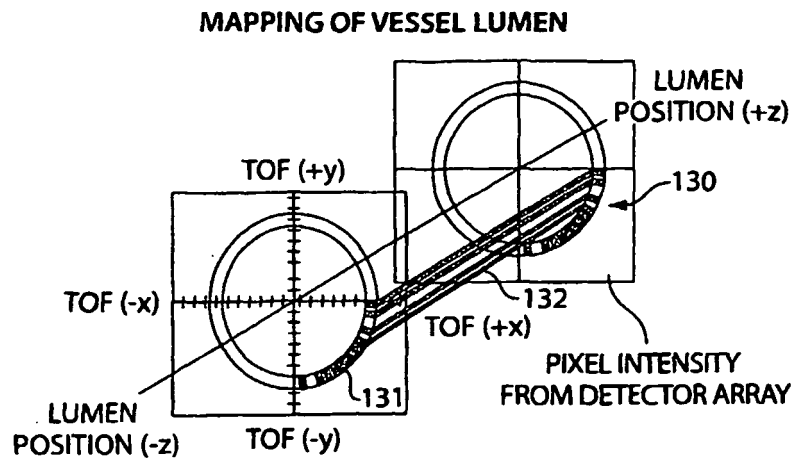


COAXIAL OR MULTIMODE FIBER: CENTRAL CORE CARRIES VISIBLE, NearIR AND FREQUENCY-ADJUSTED LIGHT FROM SOURCE OUTSIDE THE DEVICE, OUTER CORE CARRIES SCATTERED, REFLECTED OR FLUORESCENT LIGHT FROM PROBE TIP TO CONVERTER OUTSIDE INSPECTION TOOL, FIBER CLADDING IS IMPERMANENT TO LIGHT, EXCEPT FOR MICROHOLES AND DESIGNED GAPS. NANOCRYSTALS EMBEDDED IN MICROHOLES PICK UP AND AMPLIFY LIGHT SIGNAL GENERATED BY TISSUE OR PROBE.

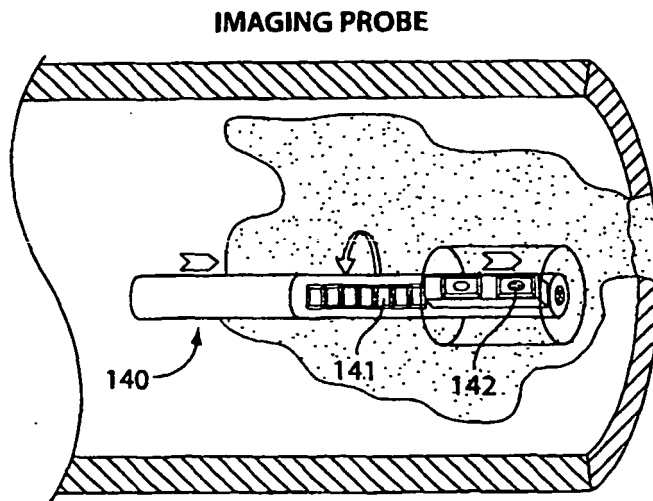
**Fig. 11**



**Fig. 12**



**Fig. 13**



**Fig. 14**

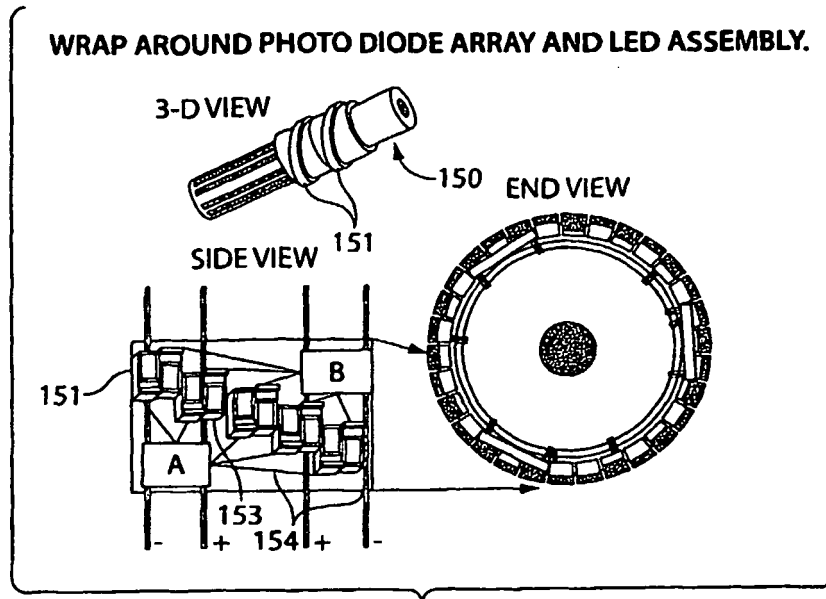


Fig. 15

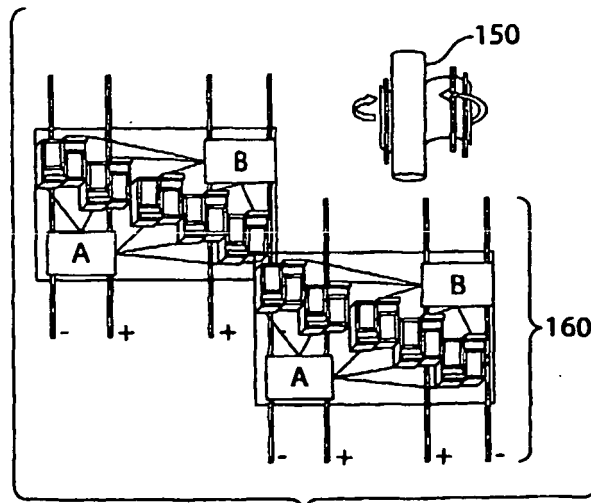


Fig. 16

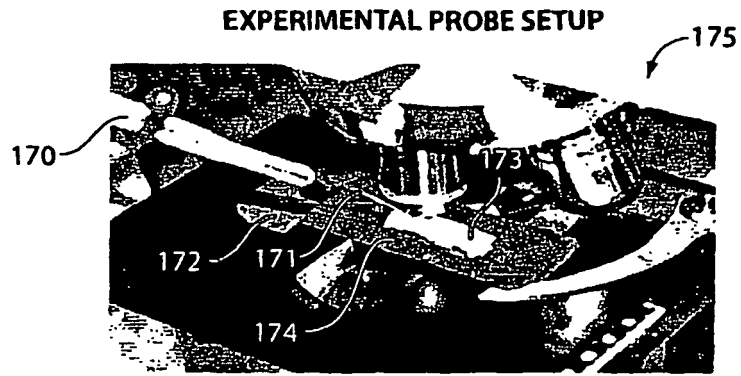
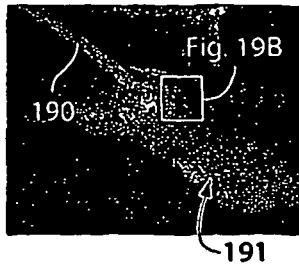


Fig. 17



Fig. 18

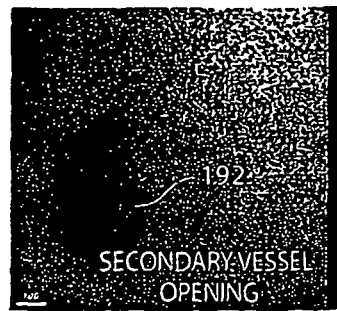
SCATTERED LIGHT IS DETECTED



PHOTOGRAPH SHOWING FIBER OPTIC PROBE ON LUMINAL SURFACE OF AORTA

Fig. 19A

SCATTERED LIGHT IS DETECTED



INTENSITY-MAPPED MICROGRAPH OF SCATTERED LIGHT. BRIGHT GREEN IS NEAREST PROBE.

Fig. 19B

PROBE ADVANCEMENT DOWN VESSEL LUMEN



Fig. 20A

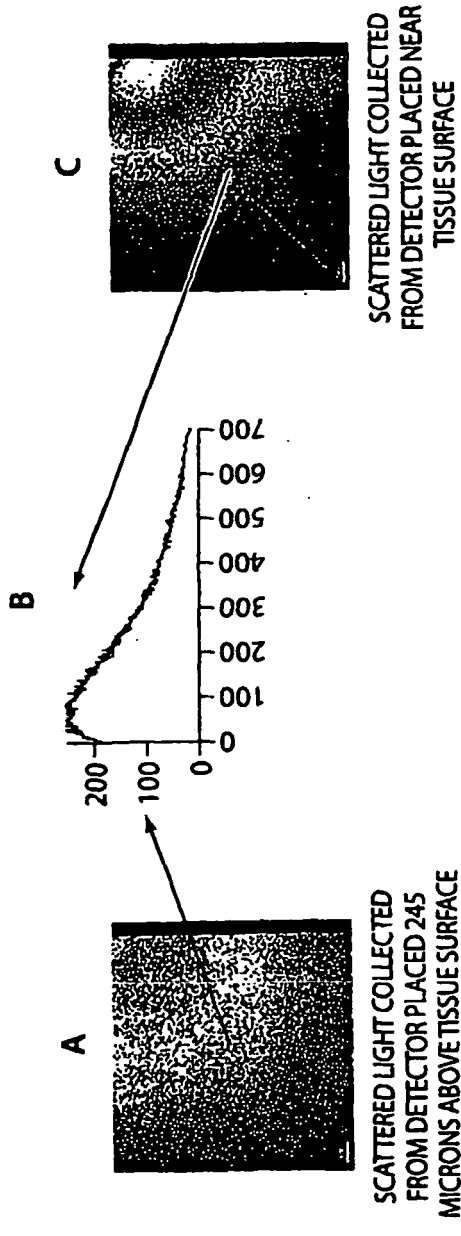
SECONDARY VESSEL LUMEN APPEARS AS A DARK BLUE STRUCTURE IN SCATTERED LIGHT SIGNAL



Fig. 20B

**SCATTERED LIGHT DETECTION IS  
INSENSITIVE TO PROBE PLACEMENT ABOVE TISSUE**

HISTOGRAM OF INTENSITY ALONG A LINE SHOWS SIMILAR PROFILE FOR BOTH POSITIONS



**Fig. 21**

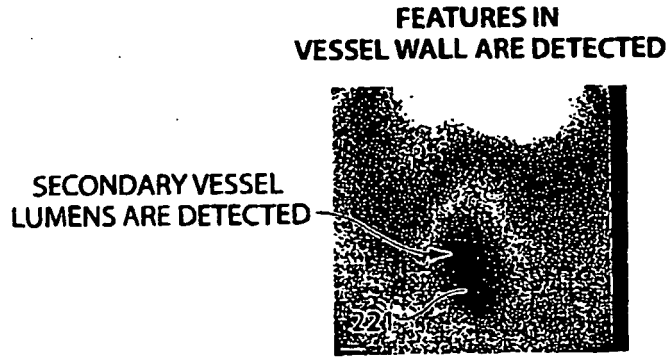


Fig. 22A

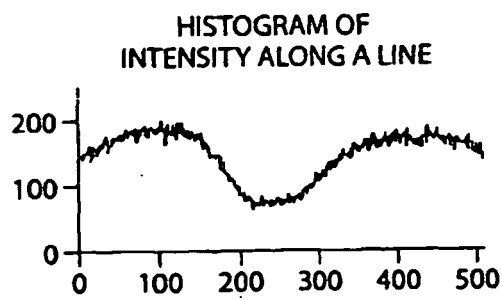


Fig. 22B

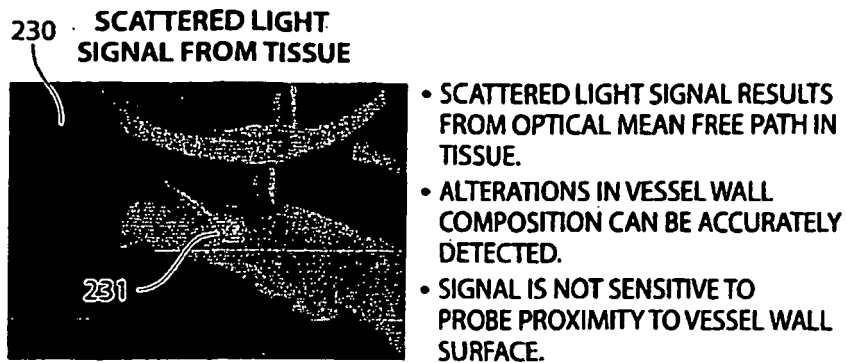


Fig. 23

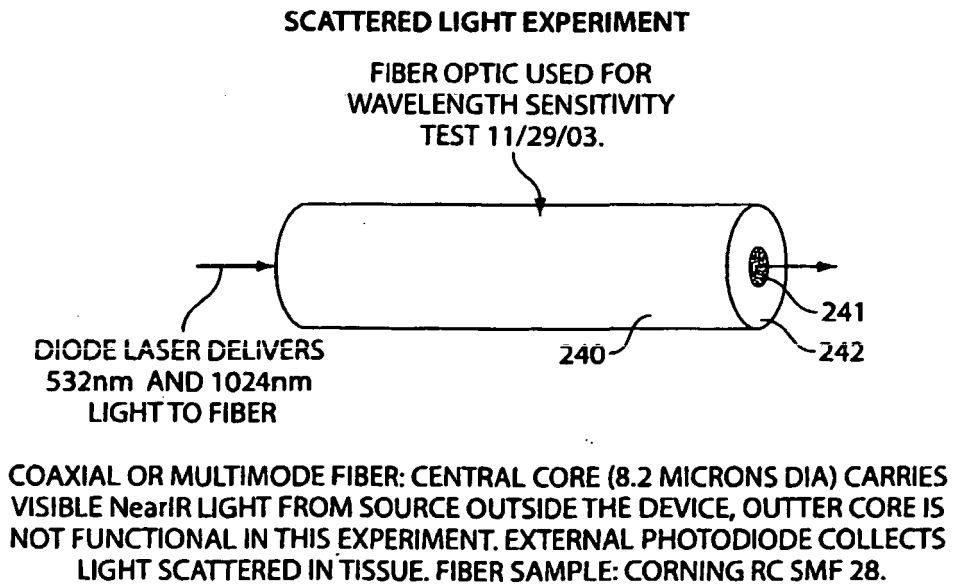


Fig. 24

EXPERIMENTAL SETUP (NOV 29, 2003)

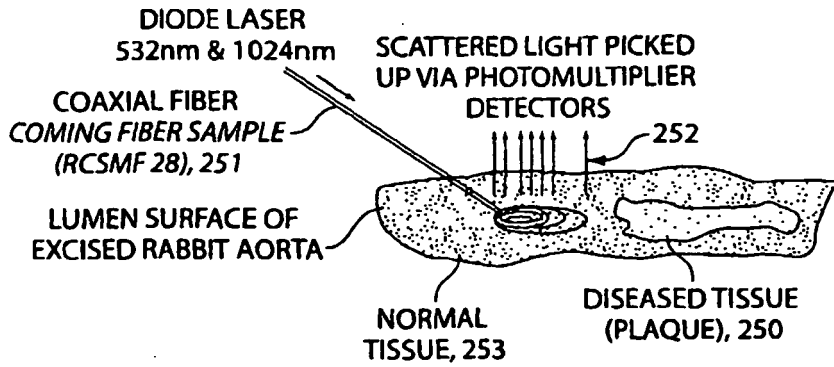


Fig. 25

DETECTION SPECTRA FROM  
AORTA (RABBIT #6, 11/15/94)

1024 nm



Fig. 26A

DETECTION SPECTRA FROM  
AORTA (RABBIT #6, 11/15/94)

532 nm



Fig. 26C

DETECTION SPECTRA FROM  
AORTA (RABBIT #6, 11/15/94)

1024 nm



Fig. 26B

DETECTION SPECTRA FROM  
AORTA (RABBIT #6, 11/15/94)

532 nm

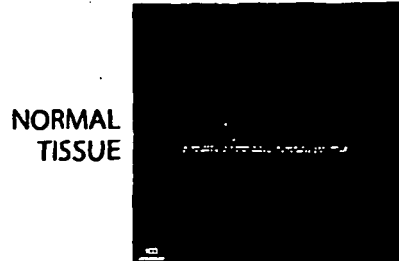


Fig. 26D

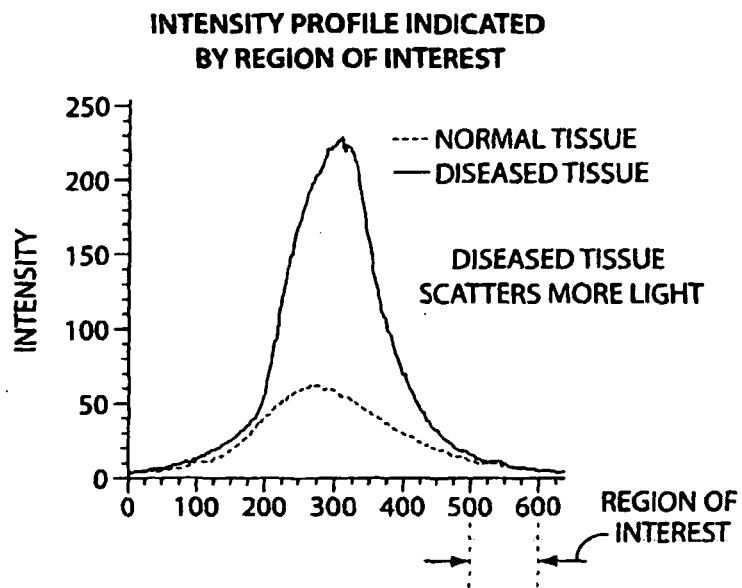


Fig. 27

**REFERENCES CITED IN THE DESCRIPTION**

*This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.*

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专利名称(译)	血管内成像装置及其用途		
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申请号	EP2005761160	申请日	2005-06-16
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[标]发明人	ROGER RICK A BRISMAR HJALMAR		
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优先权	60/580938 2004-06-18 US		
其他公开文献	EP1765172A2 EP1765172B1		
外部链接	<a href="#">Espacenet</a>		

摘要(译)

本发明涉及一种探针型成像装置，用于可视化内表面，例如表面。 ，血管腔。具体地，探针型装置对于在存在或不存在分子成像剂的情况下的直接组织成像特别有用。 本发明涉及造影剂。

Vessel Composition	Time-of-flight	Scattered Light	Reflected Light	Direct Observation
Normal	Reference	+	Reference	Reference
Plaque	+	++	++	+
Vulnerable Plaque	+	+++	+++	+