(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 485 011 B1

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
13.02.2013 Bulletin 2013/07

(21) Application number: **03714102.5**

(22) Date of filing: **11.03.2003**

(51) Int Cl.:
A61B 5/00 *(2006.01)*

(86) International application number:
PCT/US2003/007596

(87) International publication number:
WO 2003/077749 (25.09.2003 Gazette 2003/39)

(54) **MEDICAL IMAGING SYSTEMS**

MEDIZINISCHE BILDGEBUNGSSYSTEME

SYSTEMES D'IMAGERIE MEDICALE

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PT RO SE SI SK TR

(30) Priority: **12.03.2002 US 363413 P**

(43) Date of publication of application:
15.12.2004 Bulletin 2004/51

(73) Proprietor: **Beth Israel Deaconess Medical Center**
Boston, MA 02215 (US)

(72) Inventor: **FRANGIONI, John, V.**
Wayland, MA 01778 (US)

(74) Representative: **Vossius & Partner**
Siebertstrasse 4
81675 München (DE)

(56) References cited:
WO-A1-01/50955
US-A- 5 187 572
US-A- 5 255 087
US-A- 6 099 466
US-A1- 2001 007 920
US-B1- 6 289 236
US-B1- 6 293 911

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 1 485 011 B1

Printed by Jouve, 75001 PARIS (FR)

Description

Background of the Invention

[0001] Absorption and fluorescent dyes, such as indocyanine green, have proven useful for medical imaging applications. Some of the more commonly used dyes share a number of useful characteristics. First, the dyes are suitable for labeling antibodies or low-molecular-weight ligands of diagnostic significance, or otherwise adapted for sequestration or preferential uptake at a site of interest such as a lesion. The dyes are safe for injection or other introduction into a live subject. And finally, the dyes emit light at a specific wavelength when excited, so that their location and concentration may be tracked.

[0002] A number of imaging systems have been devised to detect and display these dyes within living tissue. For example, dyes such as indocyanine green have been used to visualize blood flow in eyes. In some cases, such as U.S. Pat. No. 6,293,911 to Imaizumi et al., a dye imaging device has been combined with a visible light imaging system. Imaizumi describes endoscopic tools that generate images of dye-labeled antibodies superimposed over visible light images captured from within the body. As a significant disadvantage, the Imaizumi system employs a number of separate cavities within an endoscopic tool for light sources and image capture, thus requiring a greater cross-sectional area for the endoscope. As a further disadvantage, the Imaizumi patent only discloses endoscopic applications, and may not be suitable for use in open surgical applications where ambient light may extend into the excitation and/or emission wavelengths of the dye.

[0003] There remains a need for improved surgical and diagnostic imaging tools capable of generating circulatory blood flow images or other functional images along with visible light images of a subject.

Summary Of The Invention

[0004] The invention is defined by the features of independent claim 1. Further preferred embodiments of the invention are defined in the dependent claims. In the following, further aspects and embodiments, which are useful for the understanding of the present invention, are discussed.

[0005] A medical imaging system provides simultaneous rendering of visible light and fluorescent images. The system may employ dyes in a small-molecule form that remains in a subject's blood stream for several minutes, allowing real-time imaging of the subject's circulatory system superimposed upon a conventional, visible light image of the subject. The system may also employ dyes or other fluorescent substances associated with antibodies, antibody fragments, or ligands that accumulate within a region of diagnostic significance. In one embodiment, the system provides an excitation light source to excite the fluorescent substance and a visible light source for general illumination within the same optical guide that is used to capture images. In another embodiment, the system is configured for use in open surgical procedures by providing an operating area that is closed to ambient light. More broadly, the systems described herein may be used in imaging applications where a visible light image may be usefully supplemented by an image formed from fluorescent emissions from a fluorescent substance that marks areas of functional interest.

[0006] The medical imaging system may include a visible light source providing light over a range of wavelengths that includes one or more wavelengths of visible light, an excitation light source providing light at one or more wavelengths outside the range of wavelengths of the visible light source, the one or more wavelengths selected to excite a fluorescent substance, which emits one or more photons at an emission wavelength; an electronic imaging device; an optical guide having a first end with a lens that captures an image of a subject and a second end that couples the image to the electronic imaging device; and a filter for coupling the visible light source and the excitation light source into the optical guide, the filter reflecting some of the light provided by the visible light source and some of the light from the excitation light source toward the subject, the filter further transmitting some visible light from the subject captured by the lens toward the electronic imaging device, and the filter further transmitting the emission wavelength from the subject captured by the lens toward the electronic imaging device.

[0007] In another embodiment, the system may include a visible light source illuminating a subject, the visible light source providing a range of wavelengths including one or more wavelengths of visible light; an excitation light source illuminating the subject, the excitation light source providing an excitation wavelength that is not one of the one or more wavelengths of visible light; a fluorescent substance introduced into a circulatory system of the subject, the fluorescent substance being soluble in blood carried by the circulatory system and the fluorescent substance emitting photons at an emission wavelength in response to the excitation wavelength; an electronic imaging device that captures an image of a field of view that includes some portion of the subject and the circulatory system of the subject, the image including a first image obtained from the one or more wavelengths of visible light and a second image obtained from the emission wavelength; and a display that renders the first image and the second image, the second image being displayed at a visible light wavelength.

[0008] In another embodiment, the system may include an operating area closed to ambient light, the operating area including a surgical field where a surgical procedure may be performed on a subject; a visible light source illuminating the surgical field, the visible light source providing a range of wavelengths including one or more wavelengths of visible light; an excitation light source illuminating the surgical field, the excitation light source including at least one wavelength outside the range of wavelengths of visible light; a fluorescent substance suitable for in vivo use, the fluorescent substance fluorescing at an emission wavelength in response to the at least one wavelength of the excitation light source, the fluorescent substance being introduced into the surgical field; an electronic imaging device that captures a visible light image of the surgical field and an emission wavelength image of the surgical field; and a display that renders the visible light image and the emission wavelength image of the surgical field, the emission wavelength image being displayed at a visible light wavelength.

[0009] In another embodiment, the system may include a visible light source that illuminates a subject, the visible light source providing a range of wavelengths including one or more wavelengths of visible light; an excitation light source that illuminates the subject at the same time that the visible light source illuminates the subject, the excitation light source providing an excitation wavelength that is not one of the one or more wavelengths of visible light; a fluorescent substance introduced into a circulatory system of the subject, the fluorescent substance being soluble in blood carried by the circulatory system and the fluorescent substance emitting photons at an emission wavelength in response to the excitation wavelength; and an electronic imaging device that captures an image of a field of view that includes some portion of the subject and the circulatory system of the subject, the image including a first image obtained from the one or more wavelengths of visible light and a second image concurrently obtained from the emission wavelength.

[0010] In the embodiments above, the one or more wavelengths of visible light from the visible light source may exclude far-red light, at least one of the excitation light source and the emission wavelength including a far-red light wavelength. The filter may be a dichroic mirror placed in the optical guide at a forty-five degree angle to a central axis of the optical guide.

[0011] The system may include a second filter. The second filter may separate the emission wavelength from the range of wavelengths from the visible light source, the emission wavelength being directed toward a first optical transducer of the electronic imaging device and the range of wavelengths from the visible light source being directed toward a second optical transducer of the electronic imaging device. The second filter may separate the emission wavelength from the range of wavelengths from the visible light source, the emission wavelength being directed toward a first optical transducer of the electronic imaging device and the range of wavelengths from the visible light source being directed toward a second optical transducer of the electronic imaging device wherein the second optical transducer separately senses at least each one of red, green, and blue light intensities. The second filter may separate the emission wavelength from the range of wavelengths from the visible light source, the emission wavelength being directed toward a first optical transducer of the electronic imaging device and the range of wavelengths from the visible light source being directed toward a second optical transducer of the electronic imaging device wherein the second optical transducer separately senses at least each one of cyan, magenta, and yellow light intensities. The second filter may separate the emission wavelength from the range of wavelengths from the visible light source, the emission wavelength being directed toward a first optical transducer of the electronic imaging device and the range of wavelengths from the visible light source being directed toward a second optical transducer of the electronic imaging device wherein the second filter includes a dichroic mirror that reflects the emission wavelength and transmits the one or more wavelengths of visible light from the visible light source. The second filter may separate the emission wavelength from the range of wavelengths from the visible light source, the emission wavelength being directed toward a first optical transducer of the electronic imaging device and the range of wavelengths from the visible light source being directed toward a second optical transducer of the electronic imaging device wherein the second filter includes a dichroic mirror that reflects the one or more wavelengths of visible light from the visible light source and transmits the emission wavelength. The second filter may shape the wavelengths of the visible light source.

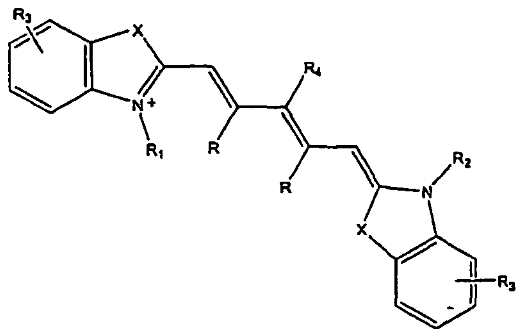
[0012] The electronic imaging device may include at least one charge-coupled device. The excitation light source may include a laser. The electronic imaging device may include a video camera sensitive to visible light the electronic imaging device may include an emission wavelength camera. The electronic imaging device may capture a visible light image and an emission wavelength image, the system further including a processor that converts the emission wavelength image to a converted image having one or more visible light components, and combines the converted image with the visible light image for display. The electronic imaging device may capture a visible light image and an emission wavelength image, the system further including a processor that converts the emission wavelength image to a converted image having one or more visible light components, and superimposes the converted image onto the visible light image for display.

[0013] The electronic imaging device may capture a visible light image and an emission wavelength image, the visible light image being captured at thirty frames per second and the emission wavelength being captured at fifteen frames per second, the emission wavelength being converted to thirty frames per second for combination with the visible light image. The electronic imaging device may capture a visible light image and an emission wavelength image, wherein the visible light image is captured at thirty frames per second and the emission wavelength is captured at fifteen frames per second, the visible light image being converted to fifteen frames per second for combination with the emission wavelength image.

[0014] The system may include a display that displays images captured by the electronic imaging device. The display may be provided to a physician for use during a procedure, the procedure being at least one of a diagnostic procedure or a therapeutic procedure. The display may include a surgical microscope.

[0015] The fluorescent substance may label at least one of an antibody, an antibody fragment, or a low-molecular-weight ligand that accumulates at a lesion, the system being used to visualize the lesion. The fluorescent substance may be soluble in blood, the system being used to visualize a blood system. The display may render the second image of the circulatory system superimposed on the first image of the subject. The fluorescent substance may be a fluorescent dye injected into the subject by an intravenous injection. The fluorescent substance may be sprayed onto the subject. The fluorescent substance may be one or more quantum dots. The fluorescent substance may include at least one of indocyanine green; fluorescein; methylene blue, and IRDye78-CA.

[0016] The fluorescent substance may be a dye having a structure of the formula:



wherein, as valence and stability permit,

X represents $C(R)_2$, S, Se, O, or NR_5;
R represents H or lower alkyl, or two occurrences of R, taken together, form a ring together with the carbon atoms through which they are connected;
R_1 and R_2 represent, independently, substituted or unsubstituted lower alkyl, lower alkenyl, cycloalkyl, cycloalkylalkyl, aryl, or aralkyl;
R_3 represents, independently for each occurrence, one or more substituents to the ring to which it is attached;
R_4 represents H, halogen, or a substituted or unsubstituted ether or thioether of phenol or thiophenol; and
R_5 represents, independently for each occurrence, substituted or unsubstituted lower alkyl, cycloalkyl, cycloalkylalkyl, aryl, or aralkyl.

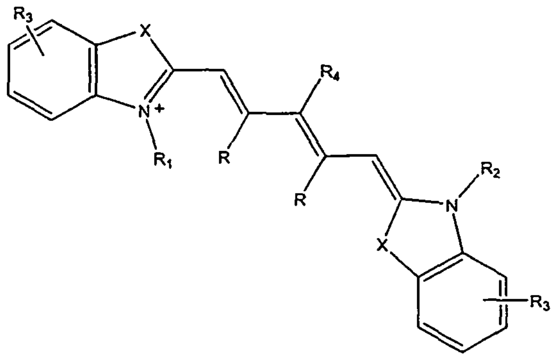
[0017] The methods as described herein may be performed with the systems according to the present invention and may include illuminating a subject with one or more wavelengths of visible light; concurrently illuminating the subject with an excitation wavelength that is not one of the one or more wavelengths of visible light; introducing a fluorescent substance into a circulatory system of the subject, the fluorescent substance being soluble in blood carried by the circulatory system and the fluorescent substance emitting photons at an emission wavelength in response to the excitation wavelength; electronically capturing a visible light image of the subject; electronically capturing an emission wavelength image of the subject that shows the circulatory system; and displaying concurrently the visible light image of the subject and the emission wavelength image of the circulatory system.

[0018] In another embodiment, a method as described herein may include: enclosing a subject in an operating area closed to ambient light; illuminating the subject with one or more wavelengths of visible light; concurrently illuminating the subject with an excitation wavelength that is not one of the one or more wavelengths of visible light; introducing a fluorescent substance into the subject, the fluorescent substance emitting photons at an emission wavelength in response to the excitation wavelength; electronically capturing a visible light image of the subject; electronically capturing an emission wavelength image of the subject; and displaying concurrently the visible light image and the emission wavelength.

[0019] In another embodiment, a method described herein may include: providing one or more wavelengths of visible light; providing an excitation wavelength that is not one of the one or more wavelengths of visible light; introducing a fluorescent substance into a subject, the fluorescent substance emitting photons at an emission wavelength in response to the excitation wavelength; providing a laparoscope having a first optical path that directs the one or more wavelengths of visible light toward a subject, a second optical path that directs the excitation wavelength toward the subject, and a third optical path that directs an emission wavelength and the one or more wavelengths of visible light from the subject to an imaging device; making an incision in a body that includes the subject; directing the laparoscope into the incision so that the subject is within a field of view of the laparoscope; and displaying concurrently a visible light image of the subject and the emission wavelength image of the subject. At least two of the first optical path, the second optical path, and the third optical path may be coaxial.

[0020] In another embodiment, a method described herein may include: providing one or more wavelengths of visible light; providing an excitation wavelength that is not one of the one or more wavelengths of visible light; introducing a fluorescent substance into a subject, the fluorescent substance emitting photons at an emission wavelength in response to the excitation wavelength; providing an endoscope having an optical path for directing images of the subject to an imaging device; coupling the excitation wavelength and the one or more wavelengths of visible light into the optical path; directing the endoscope into a body so that the subject is within a field of view of the endoscope; capturing an emission wavelength image of the subject and a visible light image of the subject at the imaging device; and displaying concurrently the visible light image of the subject and the emission wavelength image of the subject.

[0021] The fluorescent substance may be a dye having a structure of the formula:



wherein, as valence and stability permit,

X represents $C(R)_2$, S, Se, O, or NR_5;
R represents H or lower alkyl, or two occurrences of R, taken together, form a ring together with the carbon atoms through which they are connected;
R_1 and R_2 represent, independently, substituted or unsubstituted lower alkyl, lower alkenyl, cycloalkyl, cycloalkylalhyl, aryl, or aralkyl;
R_3 represents, independently for each occurrence, one or more substituents to the ring to which it is attached;
R_4 represents H, halogen, or a substituted or unsubstituted ether or thioether of phenol or thiophenol; and
R_5 represents, independently for each occurrence, substituted or unsubstituted lower alkyl, cycloalkyl, cycloalkylalkyl, aryl, or aralkyl.

Brief Description Of Drawings

[0022] The invention will be appreciated more fully from the following further description thereof, with reference to the accompanying drawings, wherein:

Fig. 1 shows an embodiment of an imaging system of the present invention for use during open surgery;
Fig. 2 shows a near-infrared window used by the imaging system;
Fig. 3 shows an embodiment of an imaging system for use in an endoscopic tool which is not part of the present invention; and
Fig. 4 shows an image displaying both a circulatory system and surrounding tissue.

Detailed Description of Certain Embodiments of the Invention

[0023] To provide an overall understanding of the invention, certain illustrative embodiments which are either part of the invention or useful for understanding the present invention will now be described, including a system for generating superimposed circulatory and tissue images in video format. However, it will be understood that the methods and systems described herein can be suitably adapted to other medical imaging applications where visible light tissue images may be usefully displayed with diagnostic image information obtained from outside the visible light range and superimposed onto the visible light image. More generally, the methods and systems described herein may be adapted to any imaging application where a visible light image may be usefully displayed with a superimposed image captured from areas within the visible light image that are functionally marked to emit photons outside the visible light range by a dye or other material. For example, the systems and methods are applicable to a wide range of diagnostic or surgical applications where a target pathology, tissue type, or cell may be labeled with a fluorescent dye or other fluorescent substance. The invention is defined by the features of the claims.

[0024] Figure 1 shows an embodiment of an imaging system for use during open surgery. The imaging system 100 may include a visible light source 102, and excitation light source 104, a surgical field 106, a dye source 108 containing a dye 110, a lens 112, a first filter 114, a second filter 116, a third filter 118, a near-infrared camera 120, a video camera 122, an image processing unit 124, and a display 126. In general, the visible light source 102 and the excitation light source 104 illuminate the surgical field 106. The dye 110 may be introduced from the dye source 108, such as through injection into the bloodstream of a subject. An image from the surgical field 106 is then captured by two cameras, the video camera 122 capturing a conventional, visible light image of the surgical field 106 and the near-infrared camera 120 capturing a diagnostic image based upon the distribution of the dye 110 in the surgical field 106. These images may be combined by the image processing unit 124 and presented on a display 126 where they may be used, for example, by a surgeon conducting a surgical procedure. Each aspect of the system 100 is now described in more detail.

[0025] The imaging system 100 may be surrounded by an operating area (not shown) closed to ambient light. As will become clear from the following, many visible light sources such as incandescent lamps, halogen lamps, or daylight may include a broad spectrum of electromagnetic radiation that extends beyond the range of visible light detected by the human eye and into wavelengths used in the present system as a separate optical channel for generating diagnostic images. In order to effectively detect emission in these super-visible light wavelengths, it is preferred to enclose the surgical field 106, light sources 102, 104, and cameras 120, 122 in an area that is not exposed to broadband light sources. This may be achieved by using an operating room closed to external light sources, or by using a hood or other enclosure or covering for the surgical field 106 that prevents invasion by unwanted spectrum. The visible light source 102 may then serve as a light source for the visible light camera 122, and also for provide conventional lighting within the visible light spectrum. As used herein, the term "operating area" is intended specifically to refer to an open surgical site that is closed to ambient light. Endoscopic or laparoscopic applications, as described below, are confined to surgical procedures within a closed body cavity, and do not include an operating area as that term is intended herein.

[0026] The visible light source 102 may be, for example, a near-infrared depleted white light source. This may be a one-hundred fifty Watt halogen lamp with one or more filters to deplete wavelengths greater than 700 nanometers ("nm"). Generally, any light source constrained to wavelengths between 400 nm and 700 nm may operate as the visible light source 102. In certain applications, the excitation light source 104 and resulting emission from the dye 110 may have wavelengths near or below 700 nm, as with Cy5 dye, which emits light when excited at 650 nm. These near-red dyes may be used with the present system, however, this requires a visible light source 102 that excludes a portion of the visible light spectrum in which the dye operates, i.e., a far-red depleted white light source. Similarly, applications using quantum dots as a fluorescent substance may have absorption or emission wavelengths anywhere in the visible light spectrum, and a suitable visible light source should be depleted at the wavelength(s) of interest. As such, the visible light source 102 should more generally be understood to be a source of light that includes some, but not necessarily all, of the wavelengths of visible light.

[0027] It should also be understood that, in a far-red imaging system or infrared imaging system such as those noted above, the near-infrared camera 120 described in the example embodiment will instead be a camera sensitive to the emission wavelength of the dye 110 or other fluorescent substance, and that other modifications to light sources, filters and other optics will be appropriate. Similar modifications may be made to isolate a band of wavelengths for dye excitation and emission anywhere within or outside the visible light range, provided that suitable optics, cameras, and dyes are available. Other fluorescent substances may also be used. For example, quantum dots may emit at visible light wavelengths, far-red, near-infrared, and infrared wavelengths, and at other wavelengths, typically in response to absorption below their emission wavelength. Suitable adjustments will be made to the excitation light source 104 and the emission camera, the near-infrared camera 120 in the example embodiment, for such applications. Cameras sensitive to far-red, near-infrared, and infrared wavelengths are commercially available.

[0028] The excitation light source 104 provides light at a wavelength that excites the dye 110. This may be, for example, a laser diode such as a 771 nm, 250 mW laser diode system, which may be obtained from Laser Components of Santa Rosa, California. Other single wavelength, narrowband, or broadband light sources may be used, provided they do not interfere with the visible light image captured by the video camera 122 or the emission wavelength of the dye 110. The near-infrared band is generally understood to include wavelengths between 700 nm and 1000 nm, and is a useful wavelength range for a number of readily available excitation light sources 104 and dyes 110 that may be used with the systems described herein. Suitable optical coupling and lenses may be provided to direct each of the visible light source 102 and the excitation light source 104 at an area of interest within the surgical field 106.

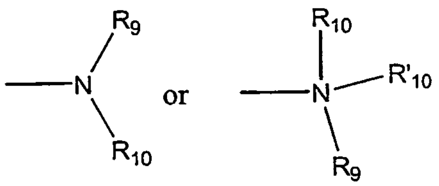
[0029] The surgical field 106 may be any area of a subject or patient that is open for a surgical procedure. This may be, for example, an open chest during a procedure such as a revascularization or cardiac gene therapy, where visualization of the circulatory system may improve identification of areas at risk for myocardial infarction. Blood flow visualization may permit an assessment of coronary arteries during a coronary artery bypass graft, or an assessment of blood flow and viability during introduction of genes for endothelial growth factor or fibroblast growth factor to induce neovascularization within ischemic regions of the heart. More generally, the surgical field 106 may include any areas of a patient's body, such as a region of the body that includes a tumor that is to be surgically removed, and that is amenable to visualization with fluourescent dyes, such as through the use of labeled antibodies.

[0030] The dye source 108 may be any instrument used for injection or other introduction of the dye 110 into a subject, such as a hypodermic needle or angiocath. Where, for example, the dye 110 is highly soluble in blood, the dye source 108 may be administered anywhere on the subject, and need not be near the surgical field 106. For example, it has been found that IRDye78-CA (the carboxylic acid form of IRDye78), when injected intravenously into a live laboratory rat, produced peak vasculature image strength of an open heart approximately 5-10 seconds after injection, and remained adequate for visualization for over one minute. In certain embodiments, the dye source 108 may not use injection. For example, the dye source 108 may spray or otherwise apply the dye 110 to an area of interest. Depending upon the type of dye and the imaging technique, the dye 110 may be delivered in a discrete dose, or may be continuously or intermittently applied and reapplied by the dye source 108.

[0031] The dye 110 may be any dye suitable for use *in vivo* and having excitation and emission wavelengths suitable for other components of the system 100. Typically, the dye 110 will be diluted to 25-50 μM for intravenous injection, such as with phosphate buffered saline, which may be supplemented with Cremophor EL (Sigma) and/or absolute ethanol. A number of suitable near-infrared dyes are described below.

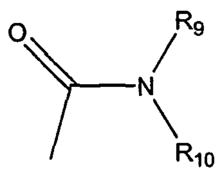
[0032] 'Acyl' refers to a group suitable for acylating a nitrogen atom to form an amide or carbamate, a carbon atom to form a ketone, a sulfur atom to form a thioester, or an oxygen atom to form an ester group, e.g., a hydrocarbon attached to a -C(=O)- moiety. Preferred acyl groups include benzoyl, acetyl, tert-butyl acetyl, pivaloyl, and trifluoroacetyl. More preferred acyl groups include acetyl and benzoyl. The most preferred acyl group is acetyl.

[0033] The terms 'amine' and 'amino' are art-recognized and refer to both unsubstituted and substituted amines as well as ammonium salts, e.g., as can be represented by the general formula:



wherein R_9, R_{10}, and R_{10} each independently represent hydrogen or a hydrocarbon substituent, or R_9 and R_{10} taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure. In preferred embodiments, none of R_9, R_{10}, and R'_{10} is acyl, e.g., R_9, R_{10}, and R'_{10} are selected from hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, carbocyclic aliphatic, and heterocyclic aliphatic. The term 'alkylamine' as used herein means an amine group, as defined above, having at least one substituted or unsubstituted alkyl attached thereto. Amino groups that are positively charged (e.g., R'_{10} is present) are referred to as 'ammonium' groups. In amino groups other than ammonium groups, the amine is preferably basic, e.g., its conjugate acid has a pK_a above 7.

[0034] The terms 'amido' and 'amide' are art-recognized as an amino-substituted carbonyl, such as a moiety that can be represented by the general formula:



wherein R_9 and R_{10} are as defined above. In certain embodiments, the amide will include imides.

[0035] 'Alkyl' refers to a saturated or unsaturated hydrocarbon chain having 1 to 18 carbon atoms, preferably 1 to 12, more preferably 1 to 6, more preferably still 1 to 4 carbon atoms. Alkyl chains may be straight (e.g., n-butyl) or branched (e.g., *sec*-butyl, isobutyl, or t-butyl). Preferred branched alkyls have one or two branches, preferably one branch. Preferred alkyls are saturated. Unsaturated alkyls have one or more double bonds and/or one or more triple bonds. Preferred unsaturated alkyls have one or two double bonds or one triple bond, more preferably one double bond. Alkyl chains may be unsubstituted or substituted with from 1 to 4 substituents. Preferred alkyl are unsubstituted. Preferred substituted alkyls are mono-, di-, or trisubstituted. Preferred alkyl substituents include halo, haloalkyl, hydroxy, aryl (e.g., phenyl, tolyl, alkoxyphenyl, alkyloxycarbonylphenyl, halophenyl), heterocyclyl, and heteroaryl.

[0036] The terms 'alkenyl' and 'alkynyl' refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond, respectively. When not otherwise indicated, the terms alkenyl and alkynyl preferably refer to lower alkenyl and lower alkynyl groups, respectively. When the term alkyl is present in a list with the terms alkenyl and alkynyl, the term alkyl refers to saturated alkyls exclusive of alkenyls and alkynyls.

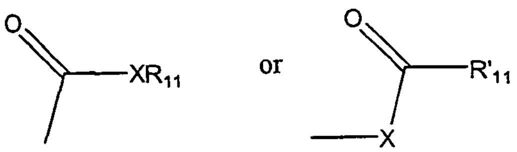
[0037] The terms 'alkoxyl' and 'alkoxy' as used herein refer to an -O-alkyl group. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy, and the like. An 'ether' is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of a hydrocarbon that renders that hydrocarbon an ether can be an alkoxyl, or another moiety such as -O-aryl, -O-heteroaryl, -O-heteroalkyl, -O-aralkyl, -O-heteroaralkyl, -O-carbocylic aliphatic, or -O-heterocyclic aliphatic.

[0038] The term 'aralkyl', as used herein, refers to an alkyl group substituted with an aryl group.

[0039] 'Aryl ring' refers to an aromatic hydrocarbon ring system. Aromatic rings are monocyclic or fused bicyclic ring systems, such as phenyl, naphthyl, etc. Monocyclic aromatic rings contain from about 5 to about 10 carbon atoms, preferably from 5 to 7 carbon atoms, and most preferably from 5 to 6 carbon atoms in the ring. Bicyclic aromatic rings contain from 8 to 12 carbon atoms, preferably 9 or 10 carbon atoms in the ring. The term 'aryl' also includes bicyclic ring systems wherein only one of the rings is aromatic, e.g., the other ring is cycloalkyl, cycloalkenyl, or heterocyclyl. Aromatic rings may be unsubstituted or substituted with from 1 to about 5 substituents on the ring. Preferred aromatic ring substituents include: halo, cyano, lower alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy, or any combination thereof. More preferred substituents include lower alkyl, cyano, halo, and haloalkyl.

[0040] 'Cycloalkyl ring' refers to a saturated or unsaturated hydrocarbon ring. Cycloalkyl rings are not aromatic. Cycloalkyl rings are monocyclic, or are fused, spiro, or bridged bicyclic ring systems. Monocyclic cycloalkyl rings contain from about 4 to about 10 carbon atoms, preferably from 4 to 7 carbon atoms, and most preferably from 5 to 6 carbon atoms in the ring. Bicyclic cycloalkyl rings contain from 8 to 12 carbon atoms, preferably from 9 to 1 0 carbon atoms in the ring. Cycloalkyl rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Preferred cycloalkyl ring substituents include halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo and haloalkyl. Preferred cycloalkyl rings include cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. More preferred cycloalkyl rings include cyclohexyl, cycloheptyl, and cyclooctyl.

[0041] The term 'carbonyl' is art-recognized and includes such moieties as can be represented by the general formula:



wherein X is a bond or represents an oxygen or a sulfur, and R_{11} represents a hydrogen, hydrocarbon substituent, or a pharmaceutically acceptable salt, $R_{11'}$ represents a hydrogen or hydrocarbon substituent. Where X is an oxygen and R_{11} or $R_{11'}$ is not hydrogen, the formula represents an 'ester'. Where X is an oxygen, and R_{11} is as defmed above, the moiety is referred to herein as a carboxyl group, and particularly when R_{11} is a hydrogen, the formula represents a 'carboxylic acid'. Where X is an oxygen, and $R_{11'}$ is hydrogen, the formula represents a 'formate'. In general, where the oxygen atom of the above formula is replaced by sulfur, the formula represents a 'thiocarbonyl' group. Where X is a sulfur and R_{11} or $R_{11'}$ is not hydrogen, the formula represents a 'thioester.' Where X is a sulfur and R_{11} is hydrogen, the formula represents a 'thiocarboxylic acid.' Where X is a sulfur and $R_{11'}$ is hydrogen, the formula represents a 'thioformate. ' On the other hand, where X is a bond, R_{11} is not hydrogen, and the carbonyl is bound to a hydrocarbon, the above formula represents a 'ketone' group. Where X is a bond, R_{11} is hydrogen, and the carbonyl is bound to a hydrocarbon, the above formula represents an 'aldehyde' or 'formyl' group.

[0042] 'Ci alkyl' is an alkyl chain having i member atoms. For example, C4 alkyls contain four carbon member atoms. C4 alkyls containing may be saturated or unsaturated with one or two double bonds (cis or trans) or one triple bond. Preferred C4 alkyls are saturated. Preferred unsaturated C4 alkyl have one double bond. C4 alkyl may be unsubstituted or substituted with one or two substituents. Preferred substituents include lower alkyl, lower heteroalkyl, cyano, halo, and haloalkyl.

[0043] 'Halogen' refers to fluoro, chloro, bromo, or iodo substituents. Preferred halo are fluoro, chloro and bromo; more preferred are chloro and fluoro.

[0044] 'Heteroalkyl' is a saturated or unsaturated chain of carbon atoms and at least one heteroatom, wherein no two heteroatoms are adjacent. Heteroalkyl chains contain from 1 to 18 member atoms (carbon and heteroatoms) in the chain, preferably 1 to 12, more preferably 1 to 6, more preferably still 1 to 4. Heteroalkyl chains may be straight or branched. Preferred branched heteroalkyl have one or two branches, preferably one branch. Preferred heteroalkyl are saturated. Unsaturated heteroalkyl have one or more double bonds and/or one or more triple bonds. Preferred unsaturated heteroalkyl have one or two double bonds or one triple bond, more preferably one double bond. Heteroalkyl chains may be unsubstituted or substituted with from 1 to about 4 substituents unless otherwise specified. Preferred heteroalkyl are unsubstituted. Preferred heteroalkyl substituents include halo, aryl (e.g., phenyl, tolyl, alkoxyphenyl, alkoxycarbonylphenyl, halophenyl), heterocyclyl, heteroaryl. For example, alkyl chains substituted with the following substituents are heteroalkyl: alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, pentoxy), aryloxy (e.g., phenoxy, chlorophenoxy, tolyloxy, methoxyphenoxy, benzyloxy, alkoxycarbonylphenoxy, acyloxyphenoxy), acyloxy (e.g., propionyloxy, benzoyloxy, acetoxy), carbamoyloxy, carboxy, mercapto, alkylthio, acylthio, arylthio (e.g., phenylthio, chlorophenylthio, alkylphenylthio, alkoxyphenylthio, benzylthio, alkoxycarbonylphenylthio), amino (e.g., amino, mono- and di- C1-C3 alkylamino, methylphenylamino, methylbenzylamino, C1-C3 alkylamido, carbamamido, ureido, guanidino).

[0045] 'Heteroatom' refers to a multivalent non-carbon atom, such as a boron, phosphorous, silicon, nitrogen, sulfur, or oxygen atom, preferably a nitrogen, sulfur, or oxygen atom. Groups containing more than one heteroatom may contain different heteroatoms.

[0046] 'Heteroaryl ring' refers to an aromatic ring system containing carbon and from 1 to about 4 heteroatoms in the ring. Heteroaromatic rings are monocyclic or fused bicyclic ring systems. Monocyclic heteroaromatic rings contain from about 5 to about 10 member atoms (carbon and heteroatoms), preferably from 5 to 7, and most preferably from 5 to 6 in the ring. Bicyclic heteroaromatic rings contain from 8 to 12 member atoms, preferably 9 or 10 member atoms in the ring. The term 'heteroaryl' also includes bicyclic ring systems wherein only one of the rings is aromatic, e.g., the other ring is cycloalkyl, cycloalkenyl, or heterocyclyl. Heteroaromatic rings may be unsubstituted or substituted with from 1 to about 4 substituents on the ring. Preferred heteroaromatic ring substituents include halo, cyano, lower alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. Preferred heteroaromatic rings include thienyl, thiazolyl, oxazolyl, pyrrolyl, purinyl, pyrimidyl, pyridyl, and furanyl. More preferred heteroaromatic rings include thienyl, furanyl, and pyridyl.

[0047] 'Heterocyclic aliphatic ring' is a non-aromatic saturated or unsaturated ring containing carbon and from 1 to about 4 heteroatoms in the ring, wherein no two heteroatoms are adjacent in the ring and preferably no carbon in the ring attached to a heteroatom also has a hydroxyl, amino, or thiol group attached to it. Heterocyclic aliphatic rings are monocyclic, or are fused or bridged bicyclic ring systems. Monocyclic heterocyclic aliphatic rings contain from about 4 to about 10 member atoms (carbon and heteroatoms), preferably from 4 to 7, and most preferably from 5 to 6 member atoms in the ring. Bicyclic heterocyclic aliphatic rings contain from 8 to 12 member atoms, preferably 9 or 10 member atoms in the ring. Heterocyclic aliphatic rings may be unsubstituted or substituted with from 1 to about 4 substituents on the ring. Preferred heterocyclic aliphatic ring substituents include halo, cyano, lower alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo and haloalkyl. Heterocyclyl groups include, for example, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxathin, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, hydantoin, oxazoline, imidazolinetrione, triazolinone, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, quinoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. Preferred heterocyclic aliphatic rings include piperazyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and piperidyl. Heterocycles can also be polycycles.

[0048] The term 'hydroxyl' means -OH.

[0049] 'Lower alkyl' refers to an alkyl chain comprised of 1 to 4, preferably 1 to 3 carbon member atoms, more preferably 1 or 2 carbon member atoms. Lower alkyls may be saturated or unsaturated. Preferred lower alkyls are saturated. Lower alkyl may be unsubstituted or substituted with one or about two substituents. Preferred substituents on lower alkyl include cyano, halo, trifluoromethyl, amino, and hydroxyl. Throughout the application, preferred alkyl groups are lower alkyls. In preferred embodiments, a substituent designated herein as alkyl is a lower alkyl. Likewise, 'lower alkenyl' and 'lower alkynyl' have similar chain lengths.

[0050] 'Lower heteroalkyl' refers to a heteroalkyl chain comprised of 1 to 4, preferably 1 to 3 member atoms, more preferably 1 to 2 member atoms. Lower heteroalkyl contain one or two non-adjacent heteroatom member atoms. Preferred lower heteroalkyl contain one heteroatom member atom. Lower heteroalkyl may be saturated or unsaturated. Preferred lower heteroalkyl are saturated. Lower heteroalkyl may be unsubstituted or substituted with one or about two substituents. Preferred substituents on lower heteroalkyl include cyano, halo, trifluoromethyl, and hydroxyl.

[0051] 'Mi heteroalkyl' is a heteroalkyl chain having i member atoms. For example, M4 heteroalkyls contain one or two non-adjacent heteroatom member atoms. M4 heteroalkyls containing 1 heteroatom member atom may be saturated or unsaturated with one double bond (cis or trans) or one triple bond. Preferred M4 heteroalkyl containing 2 heteroatom member atoms are saturated. Preferred unsaturated M4 heteroalkyl have one double bond. M4 heteroalkyl may be unsubstituted or substituted with one or two substituents. Preferred substituents include lower alkyl, lower heteroalkyl, cyano, halo, and haloalkyl.

[0052] 'Member atom' refers to a polyvalent atom (e.g., C, O, N, or S atom) in a chain or ring system that constitutes a part of the chain or ring. For example, in cresol, six carbon atoms are member atoms of the ring and the oxygen atom and the carbon atom of the methyl substituent are not member atoms of the ring.

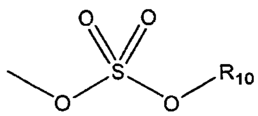
[0053] As used herein, the term 'nitro' means $-NO_2$.

[0054] 'Pharmaceutically acceptable salt' refers to a cationic salt formed at any acidic (e.g., hydroxamic or carboxylic acid) group, or an anionic salt formed at any basic (e.g., amino or guanidino) group. Such salts are well known in the art. See e.g., World Patent Publication 87/05297, Johnston et al., published September 11, 1987, incorporated herein by reference. Such salts are made by methods known to one of ordinary skill in the art. It is recognized that the skilled artisan may prefer one salt over another for improved solubility, stability, formulation ease, price and the like. Determination and optimization of such salts is within the purview of the skilled artisan's practice. Preferred cations include the alkali metals (such as sodium and potassium), and alkaline earth metals (such as magnesium and calcium) and organic cations, such as trimethylammonium, tetrabutylammonium, etc. Preferred anions include halides (such as chloride), sulfonates, carboxylates, phosphates, and the like. Clearly contemplated in such salts are addition salts that may provide an optical center where once there was none. For example, a chiral tartrate salt may be prepared from the compounds of the invention. This definition includes such chiral salts.

[0055] 'Phenyl' is a six-membered monocyclic aromatic ring that may or may not be substituted with from 1 to 5 substituents. The substituents may be located at the ortho, meta or para position on the phenyl ring, or any combination thereof. Preferred phenyl substituents include: halo, cyano, lower alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents on the phenyl ring include halo and haloalkyl. The most preferred substituent is halo.

[0056] The terms 'polycyclyl' and 'polycyclic group' refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, heteroaryls, aryls and/or heterocyclyls) in which two or more member atoms of one ring are member atoms of a second ring. Rings that are joined through non-adjacent atoms are termed 'bridged' rings, and rings that are joined through adjacent atoms are 'fused rings'.

[0057] The term 'sulfate' is art-recognized and includes a moiety that can be represented by the general formula:



in which R_{10} is as defined above.

[0058] A 'substitution' or 'substituent' on a small organic molecule generally refers to a position on a multivalent atom bound to a moiety other than hydrogen, e.g., a position on a chain or ring exclusive of the member atoms of the chain or ring. Such moieties include those defined herein and others as are known in the art, for example, halogen, alkyl, alkenyl, alkynyl, azide, haloalkyl, hydroxyl, carbonyl (such as carboxyl, alkoxycarbonyl, formyl, ketone, or acyl), thiocarbonyl (such as thioester, thioacetate, or thioformate), alkoxyl, phosphoryl, phosphonate, phosphinate, amine, amide, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfonamido, sulfonyl, silyl, ether, cycloalkyl, heterocyclyl, heteroalkyl, heteroalkenyl, and heteroalkynyl, heteroaralkyl, aralkyl, aryl or heteroaryl. It will be understood by those skilled in the art that certain substituents, such as aryl, heteroaryl, polycyclyl, alkoxy, alkylamino, alkyl, cycloalkyl, heterocyclyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl, can themselves be substituted, if appropriate. This invention is not intended to be limited in any manner by the permissible substituents of organic compounds. It will be understood that 'substitution' or 'substituted with' includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, hydrolysis, etc.

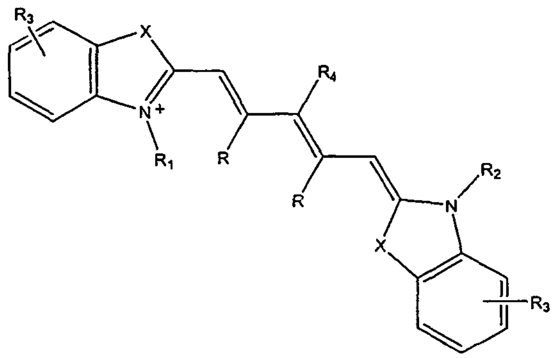
[0059] As used herein, the definition of each expression, e.g., alkyl, m, n, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

[0060] The abbreviations Me, Et, Ph, Tf, Nf, Ts, and Ms represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, nonafluorobutanesulfonyl, p-toluenesulfonyl, and methanesulfonyl, respectively. A more comprehensive list of the abbreviations utilized by organic chemists of ordinary skill in the art appears in the first issue of each volume of the *Journal of Organic Chemistry;* this list is typically presented in a table entitled Standard List of Abbreviations. The abbreviations contained in said list, and all abbreviations utilized by organic chemists of ordinary skill in the art are hereby incorporated by reference.

[0061] For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover. Also for purposes of this invention, the term 'hydrocarbon' is contemplated to include all permissible compounds or moieties having at least one carbon-hydrogen bond. In a broad aspect, the permissible hydrocarbons include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic organic compounds which can be substituted or unsubstituted.

[0062] Contemplated equivalents of the compounds described above include compounds which otherwise correspond thereto, and which have the same useful properties thereof, wherein one or more simple variations of substituents are made which do not adversely affect the efficacy of the compound. In general, the compounds of the present invention may be prepared by the methods illustrated in the general reaction schemes as, for example, described below, or by modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants that are in themselves known, but are not mentioned here.

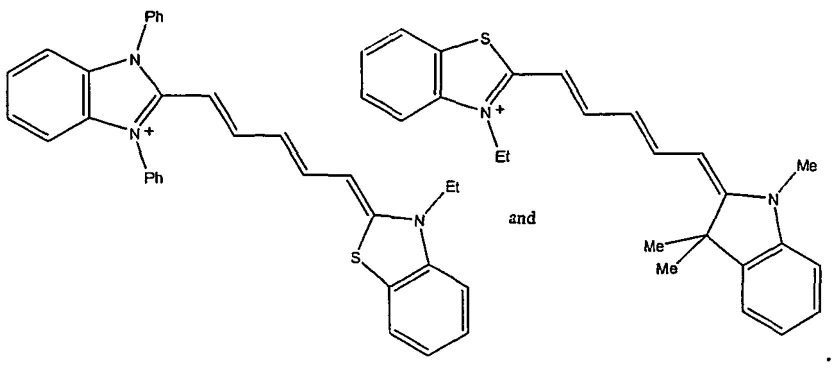
[0063] In certain embodiments, the subject method employs a fluorescent dye having a structure of the formula:



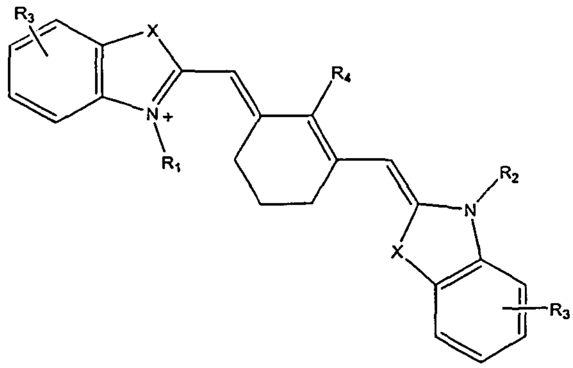
wherein, as valence and stability permit,

- X represents $C(R)_2$, S, Se, O, or NR_5;
- R represents H or lower alkyl, or two occurrences of R, taken together, form a ring together with the carbon atoms through which they are connected;
- R_1 and R_2 represent, independently, substituted or unsubstituted lower alkyl, lower alkenyl, cycloalkyl, cycloalkylalkyl, aryl, or aralkyl, e.g., optionally substituted by sulfate, phosphate, sulfonate, phosphonate, halogen, hydroxyl, amino, cyano, nitro, carboxylic acid, amide, etc., or a pharmaceutically acceptable salt thereof;
- R_3 represents, independently for each occurrence, one or more substituents to the ring to which it is attached, such as a fused ring (e.g., a benzo ring), sulfate, phosphate, sulfonate, phosphonate, halogen, lower alkyl, hydroxyl, amino, cyano, nitro, carboxylic acid, amide, etc., or a pharmaceutically acceptable salt thereof;
- R_4 represents H, halogen, or a substituted or unsubstituted ether or thioether of phenol or thiophenol; and
- R_5 represents, independently for each occurrence, substituted or unsubstituted lower alkyl, cycloalkyl, cycloalkylalkyl, aryl, or aralkyl, e.g., optionally substituted by sulfate, phosphate, sulfonate, phosphonate, halogen, hydroxyl, amino, cyano, nitro, carboxylic acid, amide, etc., or a pharmaceutically acceptable salt thereof.

[0064] Dyes representative of this formula include indocyanine green, as well as:



[0065] In certain embodiments wherein two occurrences of R taken together form a ring, the ring is six-membered, e.g., the fluorescent dye has a structure of formula:



wherein X, R_1, R_2, R_3, R_4, and R_5 represent substituents as described above.

[0066] Dyes representative of this formula include IRDye78, IRDye80, IRDye38, IRDye40, IRDye41, IRDye700, IRDye800, Cy7 (AP Biotech), and compounds formed by conjugating a second molecule to any such dye, e.g., a protein or nucleic acid conjugated to IRDye800, IRDye40, or Cy7, etc. The IRDyes are commercially available from Li-Cor Biosciences of Lincoln, Nebraska, and each dye has a specified peak absorption wavelength (also referred to herein as the excitation wavelength) and peak emission wavelength that may be used to select suitable optical hardware for use therewith. It will be appreciated that other dyes may also be used, including the far-red dyes noted above, provided suitable adjustments are made to the visible light imaging components of the system 100, and other near-infrared dyes or infrared substances such as the previously mentioned quantum dots. Several specific dyes suited for specific imaging techniques are now described.

[0067] IRDye78-CA is useful for imaging the vasculature of the tissues and organs. The dye in its small molecule form is soluble in blood, and has an *in vivo* early half-life of several minutes. This permits multiple injections during a single procedure. Indocyanine green has similar characteristics, but is somewhat less soluble in blood and has a shorter half-life. IRDye78 may also be used in other imaging applications, since it can be conjugated to tumor-specific ligands for tumor visualization. More generally, IRDye78 may be linked to an antibody, antibody fragment, or ligand associated with a tumor. Presence of the tumor or lesion may then be visualized using the techniques described above.

[0068] As another example, IR-786 partitions efficiently into mitochondria and/or endoplasmic reticulum in a concentration-dependent manner, thus permitting blood flow and ischemia visualization in a living heart. The dye has been successfully applied, for example, to image blood flow in the heart of a living laboratory rat after a thoracotomy. More generally, IR-786 may be used for non-radioactive imaging of areas of ischemia in the living heart, or other visualization of the viability of other tissues.

[0069] While a number of suitable dyes have been described, it should be appreciated that such fluorescent dyes are examples only, and that more generally, any fluorescent substance may be used with the imaging systems described herein, provided the substance has an emission wavelength that does not interfere with visible light imaging. This includes the fluorescent dyes described above, as well as substances such as quantum dots which may have emission wavelengths above 1000 nm, and may be associated with an antibody, antibody fragment, or ligand and imaged *in vivo.* All such substances are referred to herein as fluorescent substances, and it will be understood that suitable modifications may be made to components of the imaging system for use with any such fluorescent substance.

[0070] The lens 112 may be any lens suitable for receiving light from the surgical field 106 and focusing the light for image capture by the near-infrared camera 120 and the video camera 122. The lens 112 may include one or more optical coatings suitable for the wavelengths to be imaged, and may provide for manual, electronically-assisted manual, or automatic control of zoom and focus.

[0071] The first filter 114 may be positioned in the image path from the lens 112 such that a visible light image having one or more visible light wavelengths is directed toward the video camera 122, either by reflection or transmittance. An emission image from the excited dye 110 passes through the lens 112 and is directed toward the near infrared camera 120, again either through reflection or transmittance. A number of arrangements of the cameras 120, 122 and the first filter 114 are possible, and may involving reflecting or transmitting either the visible light image or the emission wavelength image.

[0072] In one embodiment, IRDye78-CA (carboxylic acid) having a peak absorption near 771 nm and a peak emission near 806 nm, is used with the system 100. In this embodiment, the first filter 114 may be a 785 nm dichroic mirror that transmits near-infrared light and reflects visible light. The first filter 114 may be positioned within an image path from the lens 112 such that a visible light image of the surgical field 106 is reflected toward the video camera 122 through the third filter 118. The third filter 118 may be, for example, a 400 nm - 700 nm visible light filter. At the same time, the first filter 114 is positioned with the image path from the lens 112 such that a near-infrared image (i.e., the excitation wavelength image) is transmitted toward the near-infrared camera 120 through the second filter 116. The second filter 116 may be an 810 nm +/- 20 nm near-infrared emission filter. The filters may be standard or custom-ordered optical components, which are commercially available from optical component suppliers. Other arrangements of filters and other optical components may be used with the system 100 described herein.

[0073] The near-infrared camera 120 may be any still or moving image camera suitable for capturing images at the emission wavelength of the excited dye 110. The near-infrared camera may be, for example, an Orca-ER near-infrared camera with settings of gain 7, 2 x 2 binning, 640 x 480 pixel field of view, and an exposure time of 20 msec and an effective frame rate of fifteen frames per second. The Orca-ER is commercially available from Hamamatsu Photonic Systems of Bridgewater, New Jersey. It will be understood that the near-infrared camera 120 of Fig. 1 is only an example. An infrared camera, a far-red camera, or some other camera or video device may be used to capture an emission wavelength image, with the camera and any associated filters selected according to the wavelength of a corresponding fluorescent substance used with the imaging system. As used herein, the term "emission wavelength camera" is intended to refer to any such camera that may be used with the systems described herein.

[0074] The video camera 122 may be any video camera suitable for capturing images of the surgical field 106 in the visible light spectrum. In one embodiment, the video camera 122 is a color video camera model HV-D27, commercially available from Hitachi of Tarrytown, New York. The video camera 122 may capture red-green-blue (RGB) images at thirty frames per second at a resolution of 640 x 480 pixels. More generally, the near-infrared camera 120 and the video camera 122 may be any device capable of photonic detection and conversion to electronic images, including linear photodiode arrays, charge coupled device arrays, scanning photomultiplier tubes, and so forth.

[0075] The display 126 may be a television, high-definition television, computer monitor, or other display configured to receive and render signals from the image processing unit 124. The surgical field 106 may also be a neurosurgical site, with a surgical microscope used to view the surgical field 106. In this embodiment, the display 126 may be a monocular or binocular eyepiece of the surgical microscope, with the near-infrared image superimposed on the visible light image in the eyepiece. In another embodiment, the eyepiece may use direct optical coupling of the surgical field 106 to the eyepiece for conventional microscopic viewing, with the near-infrared image projected onto the eyepiece using, for example, heads-up display technology.

[0076] The image processing unit 124 may include any software and/or hardware suitable for receiving images from the cameras 120, 122, processing the images as desired, and transmitting the images to the display 126. In one embodiment, the image processing unit 124 is realized in software on a Macintosh computer equipped with a Digi-16 Snapper frame grabber for the Orca-ER, commercially available from DataCell of North Billerica, Massachussets, and equipped with a CG-7 frame grabber for the HV-D27, commercially available from Scion of Frederick Maryland, and using IPLab software, commercially available from Sanalytics of Fairfax, Virginia. While a Macintosh may be used in one embodiment, any general purpose computer may be programmed to perform the image processing functions described herein, including an Intel processor-based computer, or a computer using hardware from Sun Microsystems, Silicon Graphics, or any other microprocessor manufacturer.

[0077] Generally, the image processing unit 124 should be capable of digital filtering, gain adjustment, color balancing, and any other conventional image processing functions. The image from the near-infrared camera 120 is also typically shifted into the visible light range for display at some prominent wavelength, e.g., a color distinct from the visible light colors of the surgical field 106, so that a superimposed image will clearly depict the dye. The image processing unit 124 may also perform image processing to combine the image from the near-infrared camera 120 and the video camera 122. Where the images are displayed side-by-side, this may simply entail rendering the images in suitable locations on a computer screen. Where the images are superimposed, a frame rate adjustment may be required. That is, if the video camera 122 is capturing images at the conventional rate of thirty frames per second and the near-infrared camera 120 is taking still pictures with an effective frame rate of fifteen frames per second, some additional processing may be required to render the superimposed images concurrently. This may entail either reducing the frame rate of the video camera 122 to the frame rate of the near-infrared camera 120 either by using every other frame of video data or averaging or otherwise interpolating video data to a slower frame rate. This may instead entail increasing the frame rate of the near-infrared image data, either by holding each frame of near-infrared data over successive frames of video data or extrapolating near-infrared data, such as by warping the near-infrared image according to changes in the video image or employing other known image processing techniques.

[0078] Generally, any combination of software or hardware may be used in the image processing unit 124. The functions of the image processing unit 124 may be realized, for example, in one or more microprocessors, microcontrollers, embedded microcontrollers, programmable digital signal processors or other programmable device, along with internal and/or external memory such as read-only memory, programmable read-only memory, electronically erasable programmable read-only memory, random access memory, dynamic random access memory, double data rate random access memory, Rambus direct random access memory, flash memory, or any other volatile or non-volatile memory for storing program instructions, program data, and program output or other intermediate or final results. The functions may also, or instead, include one or more application specific integrated circuits, programmable gate arrays, programmable array logic devices, or any other device or devices that may be configured to process electronic signals. Any combination of the above circuits and components, whether packaged discretely, as a chip, as a chipset, or as a die, may be suitably adapted to use with the systems described herein.

[0079] It will further be appreciated that each function of the image processing unit 124 may be realized as computer executable code created using a structured programming language such as C, an object-oriented programming language such as C++ or Java, or any other high-level or low-level programming language that may be compiled or interpreted to run on one of the above devices, as well as heterogeneous combinations of processors, processor architectures, or combinations of different hardware and software. The image processing unit 124 may be deployed using software technologies or development environments including a mix of software languages, such as Java, C++, Oracle databases, SQL, and so forth. It will be further appreciated that the functions of the image processing unit 124 may be realized in hardware, software, or some combination of these.

[0080] In one embodiment, the visible light source 102 is a near-infrared depleted visible light source, the excitation light source 104 is a 771 nm, 250 mW laser diode, the dye 110 is indocyanine green or IRDye78-CA, the first filter 114 is a 785 nm dichroic mirror configured to transmit near-infrared light and reflect visible light, the second filter 116 is an 810 nm +/- 20 nm near-infrared emission filter, and the third filter 118 is a 400 nm to 700 nm filter. The image processing unit 124 is a computer with software for image capture from the near-infrared camera 120 and the video camera 122, for making suitable color adjustment to the images from the near-infrared camera 120, for making frame rate adjustments to the video camera 122 image, and for combining the two images for superimposed display on the display 126.

[0081] The systems described above have numerous surgical applications. For example, the system may be deployed as an aid to cardiac surgery, where it may be used intraoperatively for direct visualization of cardiac blood flow, for direct visualization of myocardium at risk for infarction, and for image-guided placement of gene therapy and other medicinals to areas of interest. The system may be deployed as an aid to oncological surgery, where it may be used for direct visualization of tumor cells in a surgical field or for image-guided placement of gene therapy and other medicinals to an area of interest. The system may be deployed as an aid to general surgery for direct visualization of any function amenable to imaging with fluorescent dyes, including blood flow and tissue viability. In dermatology, the system may be used for sensitive detection of malignant cells or other skin conditions, and for non-surgical diagnosis of dermatological diseases using near-infrared ligands and/or antibodies.

[0082] Figure 2 shows a near-infrared window used by the imaging system. The near-infrared window 200 is characterized by wavelengths where absorbance is at a minimum. The components of living tissue with significant near-infrared absorbance include water 204, lipid 208, oxygenated hemoglobin 210, and deoxygenated hemoglobin 212. As shown in Fig. 2, oxygenated hemoglobin 210 and deoxygenated hemoglobin have significant absorbance below 700 nm. By contrast, lipids 208 and water 204 have significant absorbance above 900 nm. Between 700 nm and 900 nm, these absorbances reach a cumulative minimum referred to as the near-infrared window 200. While use of excitation and emission wavelengths outside the near-infrared window 200 is possible, as described in some of the examples above, fluorescence imaging within the near-infrared window 200 offers several advantages including low tissue autofluorescence, minimized tissue scatter, and relatively deep penetration depths. While the near-infrared window 200 is one useful wavelength range for imaging, the systems described herein are not limited to either excitation or emission wavelengths in this window, and may employ, for example, far-red light wavelengths below the near-infrared window 200, or infrared light wavelengths above the near-infrared window 200, both of which may be captured using commercially available imaging equipment.

[0083] Figure 3 shows an embodiment of an imaging system for use in an endoscopic tool. The imaging system 300 may include a visible light source 302, and excitation light source 304, a surgical field 306, a dye source 308 containing a dye 310, a lens 312, a first filter 314, a second filter 316, a third filter 318, a near-infrared camera 320, a video camera 322, an image processing unit 324, and a display 326. In general, the visible light source 302 and the excitation light source 304 illuminate the surgical field 306. The dye 310 may be introduced from the dye source 308, such as through injection into the bloodstream of a subject. An image from the surgical field 306 is then captured by two cameras, the video camera 322 capturing a conventional, visible light image of the surgical field 306 and the near-infrared camera 320 capturing a diagnostic image based upon the distribution of the dye 310 in the surgical field 306. These images may be combined by the image processing unit 324 and presented on a display 326 where they may be used, for example, by a surgeon conducting a surgical procedure. In general, each of these components may be any of those components similarly described with reference to Fig. 1 above. Differences for an endoscopic tool are now described.

[0084] The imaging system 300 for use as an endoscopic tool may further include a first lens/collimator 303 for the visible light source, a second lens/collimator 305 for the excitation light source 304, an optical coupler 307 that combines the excitation light and the visible light, a dichroic mirror 309, and an endoscope 311 having a first cavity 313 and a second cavity 315.

[0085] The first lens/collimator 303, the second lens/collimator 305, and the optical coupler 307 serve to combine the excitation light and the visible light into a single light source. This light source is coupled into the first cavity 313 through the dichroic mirror 309. In one embodiment, the dichroic mirror 309 preferably provides fifty percent reflection of light having wavelengths from 400 nm to 700 nm, in order to optimize an intensity of visible light that reaches the video camera

322 after illuminating the surgical field 306 and passing through the dichroic mirror 309 on its return path to the video camera 322. The dichroic mirror 309 also preferably has greater than ninety percent reflection of wavelength from the excitation light source 304, such as between 700 nm and 785 nm, so that these wavelengths are not transmitted to the cameras 320, 322 after reflecting off the surgical field. Using this arrangement, visible and excitation light sources 302, 304 share the first cavity 313 of the endoscope with the return light path for a visible light image and an emission wavelength image.

[0086] The second cavity 315 of the endoscope 311 may be provided for insertion of a tool, such as an optical tool like a laser for irradiation of a site in the surgical field 306, or a physical tool like an instrument for taking a biopsy of tissue within the surgical field. By combining the optical paths of the imaging system 300 within a single cavity of the endoscope 311, the combined gauge of the first cavity 313 for imaging and the second cavity 315 may be advantageously reduced.

[0087] The imaging system 300 may instead be used with a laparoscope. Typically, a laparoscope is inserted into a body cavity through an incision, as distinguished from an endoscope which is inserted through an existing body opening such as the throat or rectum. A laparoscope has a different form factor than an endoscope, including different dimensional requirements. Furthermore, use of a laparascope involves at least one additional step of making an incision into a body so that the laparascope may be inserted into a body cavity. The laparoscope may be used with any of the imaging systems described above, and the imaging system 300 of Fig. 3 in particular would provide the benefit of a narrower bore for illumination and imaging optics.

[0088] It will further be appreciated that the imaging system 300 may be used to simplify imaging devices other than endoscopes and laparoscopes, such as by providing an integrated, coaxial illumination and image capture device using the techniques described above.

[0089] In addition to the surgical applications noted above in reference to Fig. 1, the endoscopic tool of Fig. 3 may be used for direct visualization of malignant or pre-malignant areas within a body cavity, or for image-guided placement of gene therapy and other medicinals to an area of interest within the body cavity.

[0090] Figure 4 shows an image displaying both a circulatory system and surrounding tissue. As described above, a visible light tissue image 402 is captured of tissue within a surgical field. As noted above, the visible light tissue image 402 may include a subset of visible light wavelengths when an optical channel for dye imaging includes a wavelength within the visible light range. A near-infrared image 404 is also captured of the same (or an overlapping) field of view of the surgical field. Although referred to here for convenience as a near-infrared image, it should be clear that the dye-based image 404 may also, or instead, employ other wavelengths, such as far-red or infrared wavelengths. The near-infrared image 404 may be shifted to a visible wavelength for display, preferably using a color that is prominent when superimposed on the visible light tissue image 402. The images 402, 404 may be frame-rate adjusted as appropriate for video display of the surgical field.

[0091] The images may be displayed separately as the visible light tissue image 402 and the near-infrared image 404. Or the images 402, 404 may be combined into a combined image 406 by the image processing unit described above. The combined image 406 may then be used as an aid to the procedures described above, or to any other surgical or diagnostic procedure that might benefit from the dye-based imaging techniques described herein.

[0092] It will be appreciated that the above functionality is merely illustrative, and that other dyes, imaging hardware, and optics may be usefully deployed with the imaging systems described herein. For example, an endoscopic tool may employ a still-image imaging system for diagnostic photography within a body cavity. Or any of the imaging systems may be used as described above with excitation and/or emission wavelengths in the far-red spectrum. Through minor adaptations that would be clear to one of ordinary skill in the art, the system could be configured to image two or more functions (i.e., tumor and blood flow) at the same time that a visible light image is captured by associating each function with a different dye having a different emission wavelength. Non-medical applications exist for the imaging system. For example, dyes in a solution form may be sprayed on a mechanical component to identify oxidation, surface defects, or the like. Dyes could also be used to track gas, steam, or air flow through a pressurized system, and in particular to identify leaks around fittings and valves.

[0093] Thus, while the invention has been disclosed in connection with the preferred embodiments shown and described in detail, various modifications and improvements thereon will become readily apparent to those skilled in the art. It should be understood that all matter contained in the above description or shown in the accompanying drawings shall be interpreted as illustrative, and not in a limiting sense.

Claims

1. A system comprising:

an enclosure for a surgical procedure adapted to exclude broadband light sources (102, 104, 302, 304) thereby

providing an operating area closed to ambient light, the operating area including a surgical field where an open surgical procedure is performable on a subject;
a visible light source (102, 302) capable of illuminating the surgical field (106), the visible light source providing a range of wavelengths including one or more wavelengths of visible light, and the visible light source (102, 302) further capable of providing conventional lighting for the surgical field (106);
an excitation light source (104, 304) capable of illuminating the surgical field, the excitation light source including at least one wavelength outside the range of wavelength of visible light;
a fluorescent substance (110, 310) suitable for in vivo use, the fluorescent substance fluorescing at an emission wavelength in response to the at least one wavelength of the excitation light source (104, 304), the fluorescent substance (110, 310) being introducible into the surgical field (106);
an electronic imaging device positioned to capture a visible light image of the surgical field and an emission wavelength image of the surgical field, the electronic imaging device including a lens (112, 312) for manual or automatic control of a focus of light received from the surgical field; and
a display (126, 326) adapted to render the visible light image and the emission wavelength image of the surgical field, the emission wavelength image being displayable at a visible light wavelength.

2. The system of claim 1, further comprising
an optical guide having a first end with a lens capture an image of the subject and a second end adapted to couple the image to the electronic imaging device; and
a first filter for coupling the visible light source (102, 302) and the excitation light source (104, 304) into the optical guide, the first filter adapted to reflect some of the light provided by the visible light source and some of the light from the excitation light source toward the subject,
the first filter further being adapted to transmit a portion of the visible light and of the emission wavelength from the subject captured by the lens (112, 312) toward the electronic imaging device.

3. The system according to any of the preceding claims, wherein the excitation light source (104, 304) is adapted to illuminate the subject at the same time that the visible light source (102, 302) illuminates the subject.

4. The system according to any of the preceding claims, wherein the one or more wavelengths of visible light from the visible light source (102, 302) do not include infrared light, and wherein at least one of the excitation light source (104, 304) and the emission wavelength includes a far-red light wavelength.

5. The system according to any of claims 2 to 4, wherein the first filter is a dichroic mirror (114, 309) placed in the optical guide at a 45° angle to a central axis of the optical guide.

6. The system of any of the preceding claims, further comprising a second filter adapted to separate/the emission wavelength from the range of wavelengths of visible light, wherein the emission wavelength is directed toward a first optical transducer of the electronic imaging device (120, 320) and the range of wavelengths of visible light is directed toward a second optical transducer (122, 322) of the electronic imaging device.

7. The system of claim 6, wherein the second optical transducer (122, 322) is sensitive to red, green, and blue light.

8. The system of claim 6, wherein the second optical transducer (122, 322) is sensitive to cyan, magenta and yellow light.

9. The system according to any of claims 6 to 8, wherein the second filter includes a dichroic mirror (114, 309) adapted to reflect the emission wavelength and transmit the one or more wavelengths of visible light.

10. The system according to any of claims 6 to 8, wherein the second filter includes a dichroic mirror adapted to reflect the one or more wavelengths of visible light and transmit the emission wavelength.

11. The system according to any of claims 6 to 8, wherein the second filter is adapted to shape the wavelengths of the visible light.

12. The system according to any of the preceding claims, wherein the electronic imaging device includes a charge-coupled device and/or a video camera and/or an emission wavelength camera.

13. The system according to any of the preceding claims, further comprising a processor adapted to convert the emission wavelength image to a converted image having one or more visible light components, and to combine the converted image with or superimpose the converted image on the visible light image for display.

14. The system according to claim 13, adapted to capture the visible light image at thirty frames per second and the emission wavelength at fifteen frames per second, and wherein either the emission wavelength is convertible to thirty frames per second or the visible light image is convertible to fifteen frames per second for combination with or superposition on the visible light image.

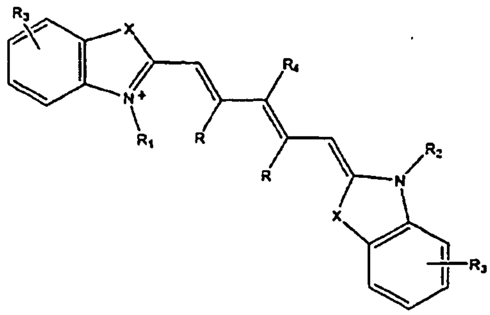
15. The system according to any of the preceding claims, wherein the excitation light source (104, 304) comprises a laser.

16. The system according to any of the preceding claims, wherein the fluorescent substance (110, 310) includes a low-molecular-weight ligand that accumulates at a lesion, the system being adapted to visualize the lesion.

17. The system according to any of the preceding claims, wherein the fluorescent substance (110, 310) includes a fluorescent dye injectable into the subject by an intravenous injection and/or a substance sprayable onto the subject.

18. The system according to any of the preceding claims, wherein the fluorescent substance (110, 310) includes at least one of indocyanine green; fluorescein; methylene blue, and IRDye78-CA.

19. The system according to any of the preceding claims, wherein the fluorescent substance (110, 310) is a dye having a structure of the formula:



wherein, as valence and stability permit,

X represents $C(R)_2$, S, Se, O, or NR_5;
R represents H or lower alkyl, or two occurrences of R, taken together, form a ring together with the carbon atoms through which they are connected;
Rand R_2 represent, independently, substituted or unsubstituted lower alkyl, lower alkenyl, cycloalkyl, cycloalkylalkyl, aryl, or aralkyl;
R_3 represents, independently for each occurrence, one or more substituents to the ring to which it is attached;
R_4 represents H, halogen, or a substituted or unsubstituted ether or thioether of phenol or thiophenol; and
R_5 represents, independently for each occurrence, substituted or unsubstituted lower alkyl, cycloalkyl, cycloalkylalkyl, aryl, or aralkyl.

20. The system according to one of the preceding claims, wherein the visible light source (102, 302) that illuminates a subject propagates along a first optical path, the excitation light source (104, 304) that illuminates the subject propagates along a second optical path, and the image from the portion of the subject propagates to the imaging device along a third optical path, wherein at least two of the first optical path, the second optical path, and the third optical path are coaxial.

21. The system according to one of the preceding claims, wherein the display (126, 326) includes a surgical microscope.

Patentansprüche

1. System mit:

einer Umhüllung für eine chirurgische Behandlung, die eingerichtet ist, Breitbandlichtquellen (102, 104, 302, 304) auszuschließen, wodurch ein Arbeitsbereich bereitgestellt wird, der gegenüber Umgebungslicht geschlossen ist, wobei der Arbeitsbereich ein Operationsfeld umfasst, wo eine offene chirurgische Behandlung an einem Patienten durchführbar ist;

einer Quelle für sichtbares Licht (102, 302), die imstande ist, das Operationsfeld (106) zu beleuchten, wobei die Quelle für sichtbares Licht einen Wellenlängenbereich bereitstellt, der eine oder mehrere Wellenlängen des sichtbaren Lichts umfasst, und die Quelle für sichtbares Licht (102, 302) ferner imstande ist, eine herkömmliche Beleuchtung für das Operationsfeld (106) bereitzustellen;

einer Anregungslichtquelle (104, 304), die imstande ist, das Operationsfeld zu beleuchten, wobei die Anregungslichtquelle mindestens eine Wellenlänge außerhalb des Wellenlängenbereichs des sichtbaren Lichts umfasst;

einer fluoreszierenden Substanz (110, 310), die für einen In-Vivo-Gebrauch geeignet ist, wobei die fluoreszierende Substanz als Reaktion auf die mindestens eine Wellenlänge der Anregungslichtquelle (104, 304) auf einer Emissionswellenlänge fluoresziert, wobei die fluoreszierende Substanz (110, 310) in das Operationsfeld (106) einleitbar ist;

einer elektronischen Bildgebungsvorrichtung, die angeordnet ist, ein Bild im sichtbaren Licht des Operationsfelds und ein Bild der Emissionswellenlänge des Operationsfelds zu erfassen, wobei die elektronische Bildgebungsvorrichtung eine Linse (112, 312) zur manuellen oder automatischen Steuerung eines Brennpunkts des Lichts aufweist, das vom Operationsfeld empfangen wird; und

einer Anzeige (126, 326), die eingerichtet ist, das Bild des sichtbaren Lichts und das Bild der Emissionswellenlänge des Operationsfelds wiederzugeben, wobei das Bild der Emissionswellenlänge bei einer sichtbaren Lichtwellenlänge anzeigbar ist.

2. System nach Anspruch 1, das ferner aufweist:

einen optischen Leiter, der ein erstes Ende mit einer Linse, die eingerichtet ist, ein Bild des Patienten zu erfassen, und ein zweites Ende aufweist, das eingerichtet ist, das Bild in die elektronische Bildgebungsvorrichtung einzukoppeln; und

ein erstes Filter zur Einkopplung der Quelle für sichtbares Licht (102, 302) und der Anregungslichtquelle (104, 304) in den optischen Leiter, wobei das erste Filter eingerichtet ist, etwas des durch die Quelle für sichtbares Licht bereitgestellten Lichts und etwas des Lichts von der Anregungslichtquelle zum Patienten zu reflektieren, wobei das erste Filter ferner eingerichtet ist, einen Anteil des sichtbaren Lichts und der Emissionswellenlänge vom Patienten, das durch die Linse (112, 312) erfasst wird, zur elektronischen Bildgebungsvorrichtung durchzulassen.

3. System nach einem der vorhergehenden Ansprüche, wobei die Anregungslichtquelle (104, 304) eingerichtet ist, den Patienten zur selben Zeit zu beleuchten, zu der die Quelle für sichtbares Licht (102, 302) den Patienten beleuchtet.

4. System nach einem der vorhergehenden Ansprüche, wobei die eine oder die mehreren Wellenlängen des sichtbaren Lichts aus der Quelle für sichtbares Licht (102, 302) kein infrarotes Licht umfassen, und wobei die Anregungslichtquelle (104, 304) und/oder die Emissionswellenlänge eine Lichtwellenlänge im fernen Rot umfassen.

5. System nach einem der Ansprüche 2 bis 4, wobei das erste Filter ein dichroitischer Spiegel (114, 309) ist, der im optischen Leiter unter einem Winkel von 45° zu einer Mittelachse des optischen Leiters angeordnet ist.

6. System nach einem der vorhergehenden Ansprüche, das ferner ein zweites Filter aufweist, das eingerichtet ist, die Emissionswellenlänge vom Wellenlängenbereich des sichtbaren Lichts zu trennen, wobei die Emissionswellenlänge auf einen ersten optischen Wandler der elektronischen Bildgebungsvorrichtung (120, 320) gerichtet ist und der Wellenlängenbereich des sichtbaren Lichts auf einen zweiten optischen Wandler (122, 322) der elektronischen Bildgebungsvorrichtung gerichtet ist.

7. System nach Anspruch 6, wobei der zweite optische Wandler (122, 322) für rotes, grünes und blaues Licht empfindlich ist.

8. System nach Anspruch 6, wobei der zweite optische Wandler (122, 322) für cyanes, magenta und gelbes Licht empfindlich ist.

9. System nach einem der Ansprüche 6 bis 8, wobei das zweite Filter einen dichroitischen Spiegel (114, 309) aufweist, der eingerichtet ist, die Emissionswellenlänge zu reflektieren und die eine oder die mehreren Wellenlängen des sichtbaren Lichts durchzulassen.

10. System nach einem der Ansprüche 6 bis 8, wobei das zweite Filter einen dichroitischen Spiegel aufweist, der eingerichtet ist, die eine oder die mehreren Wellenlängen des sichtbaren Lichts zu reflektieren und die Emissionswellenlänge durchzulassen.

11. System nach einem der Ansprüche 6 bis 8, wobei das zweite Filter eingerichtet ist, die Wellenlängen des sichtbaren Lichts zu formen.

12. System nach einem der vorhergehenden Ansprüche, wobei die elektronische Bildgebungsvorrichtung eine ladungsgekoppelte Vorrichtung und/oder eine Videokamera und/oder eine Emissionswellenlängenkamera aufweist.

13. System nach einem der vorhergehenden Ansprüche, das ferner einen Prozessor aufweist, der eingerichtet ist, das Bild der Emissionswellenlänge in ein umgewandeltes Bild umzuwandeln, das eine oder mehrere sichtbare Lichtkomponenten aufweist, um zur Anzeige das umgewandelte Bild mit dem Bild des sichtbaren Lichts zu kombinieren oder zu überlagern.

14. System nach Anspruch 13, das eingerichtet ist, das Bild des sichtbaren Lichts mit dreißig Einzelbildern pro Sekunde und die Emissionswellenlänge mit fünfzehn Einzelbildern pro Sekunde zu erfassen, und wobei zur Kombination oder Überlagerung mit dem Bild des sichtbaren Lichts entweder die Emissionswellenlänge auf dreißig Einzelbilder pro Sekunde oder das sichtbare Licht Bild auf fünfzehn Einzelbilder pro Sekunde umsetzbar ist.

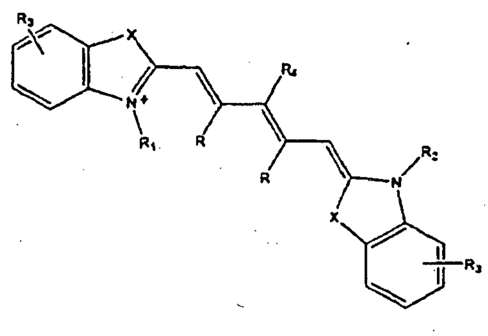
15. System nach einem der vorhergehenden Ansprüche, wobei die Anregungslichtquelle (104, 304) einen Laser aufweist.

16. System nach einem der vorhergehenden Ansprüche, wobei die fluoreszierende Substanz (110, 310) einen Liganden mit niedrigem Molekulargewicht aufweist, der sich an einer Läsion ansammelt, wobei das System eingerichtet ist, die Läsion sichtbar zu machen.

17. System nach einem der vorhergehenden Ansprüche, wobei die fluoreszierende Substanz (110, 310) einen fluoreszierenden Farbstoff, der in den Patienten durch eine intravenöse Injektion injizierbar ist, und/oder eine Substanz aufweist, die auf den Patienten sprühbar ist.

18. System nach einem der vorhergehenden Ansprüche, wobei die fluoreszierende Substanz (110, 310) mindestens eines aufweist von: Indocyaningrün; Fluorescein; Methylenblau und IRDye78-CA.

19. System nach einem der vorhergehenden Ansprüche, wobei die fluoreszierende Substanz (110, 310) ein Farbstoff ist, der die Struktur der Formel aufweist:



wobei, wenn es die Wertigkeit und Stabilität erlaubt,

X $C(R)_2$, S, Se, O oder NR_5 repräsentiert;
R H oder ein niedriges Alkyl repräsentiert, oder das zweifache Auftreten von R zusammengenommen, zusam-

men mit den Kohlenstoffatomen, durch die sie verbunden sind, einen Ring bilden;
R und R_2 unabhängig voneinander ein substituiertes oder ein unsubstituiertes niedriges Alkyl, niedriges Alkenyl, Cycloalkyl, Cycloalkylalkyl, Aryl oder Aralkyl repräsentieren;
R_3 unabhängig für jedes Auftreten einen oder mehrere Substituenten des Rings repräsentiert, an den es gebunden ist; R_4 H, Halogen oder einen substituierten oder ein unsubstituierten Ether oder Thioether von Phenol oder Thiophenol repräsentiert; und
R_5 unabhängig für jedes Auftreten ein substituiertes oder ein unsubstituiertes niedriges Alkyl, Cycloalkyl, Cycloalkylalkyl, Aryl oder Aralkyl repräsentiert.

20. System nach einem der vorhergehenden Ansprüche, wobei die Quelle für sichtbares Licht (102, 302), die einen Patienten beleuchtet, sich längs eines ersten Lichtwegs ausbreitet, die Anregungslichtquelle (104, 304), die einen Patienten beleuchtet, sich längs eines zweiten Lichtwegs ausbreitet, und sich das Bild von dem Abschnitt des Patienten zur Bildgebungsvorrichtung längs eines dritten Lichtwegs ausbreitet, wobei mindestens zwei des ersten Lichtwegs, des zweiten Lichtwegs und des dritten Lichtwegs koaxial sind.

21. System nach einem der vorhergehenden Ansprüche, wobei die Anzeige (126, 326) ein Operationsmikroskop aufweist.

Revendications

1. Système, comprenant :

une enceinte pour une opération chirurgicale, prévue pour masquer des sources de lumière à large bande (102, 104, 302, 304), en délimitant ainsi une zone opératoire fermée à la lumière environnante, ladite zone opératoire incluant un champ opératoire où il est possible de procéder à une opération chirurgicale ouverte sur un patient ;
une source de lumière visible (102, 302) apte à éclairer le champ opératoire (106), ladite source de lumière visible couvrant une plage de longueurs d'ondes comprenant une ou plusieurs longueur d'ondes de lumière visible, et la source de lumière visible (102, 302) étant en outre apte à délivrer un éclairage conventionnel pour le champ opératoire (106) ;
une source de lumière d'excitation (104, 304) apte à éclairer le champ opératoire, ladite source de lumière d'excitation comprenant au moins une longueur d'onde extérieure à la plage de longueur d'onde de lumière visible ;
une substance fluorescente (110, 310) prévue pour une utilisation in vivo, ladite substance étant fluorescente à une longueur d'onde d'émission en réaction à la longueur d'onde ou aux longueurs d'ondes de la source de lumière d'excitation (104, 304), ladite substance fluorescente (110, 310) pouvant être introduite dans le champ opératoire (106) ;
un dispositif d'imagerie électronique positionné pour enregistrer une image du champ opératoire en lumière visible et une image du champ opératoire à la longueur d'onde d'émission, ledit dispositif d'imagerie électronique comprenant une lentille (112, 312) pour la commande manuelle ou automatique d'un foyer de la lumière reçue du champ opératoire ; et
un écran (126, 326) prévu pour restituer l'image en lumière visible et l'image à la longueur d'onde d'émission du champ opératoire, l'image à la longueur d'onde d'émission étant affichable à une longueur d'onde de lumière visible.

2. Système selon la revendication 1, comprenant en outre
un guide optique présentant une première extrémité avec une lentille prévue pour saisir une image du patient et une deuxième extrémité prévue pour coupler l'image au dispositif d'imagerie électronique ; et
un premier filtre pour coupler la source de lumière visible (102, 302) et la source de lumière d'excitation (104, 304) dans le guide optique, le premier filtre étant prévu pour réfléchir une partie de la lumière délivrée par la source de lumière visible et une partie de la lumière de la source de lumière d'excitation vers le patient,
le premier filtre étant en outre prévu pour transmettre une partie de la lumière visible et de la longueur d'onde d'émission, du patient saisi par la lentille (112, 312) au dispositif d'imagerie électronique.

3. Système selon l'une quelconque des revendications précédentes, où la source de lumière d'excitation (104, 304) est prévue pour éclairer le patient simultanément à l'éclairage du patient par la source de lumière visible (102, 302).

4. Système selon l'une quelconque des revendications précédentes, où la longueur d'onde ou les longueurs d'ondes de lumière visible de la source de lumière visible (102, 302) ne comprennent pas une lumière infrarouge, et où soit la source de lumière d'excitation (104, 304), soit la longueur d'onde d'émission, soit les deux, comprennent une longueur d'onde de lumière rouge lointain.

5. Système selon l'une quelconque des revendications 2 à 4, où le premier filtre est un miroir dichroïque (114, 309) disposé dans le guide optique suivant un angle de 45° par rapport à un axe central du guide optique.

6. Système selon l'une quelconque des revendications précédentes, comprenant en outre un deuxième filtre prévu pour séparer la longueur d'onde d'émission de la plage de longueurs d'ondes de lumière visible, la longueur d'onde d'émission étant dirigée vers un premier transducteur optique du dispositif d'imagerie électronique (120, 320), et la plage de longueurs d'ondes de lumière visible étant dirigée vers un deuxième transducteur optique (122, 322) du dispositif d'imagerie électronique.

7. Système selon la revendication 6, où le deuxième transducteur optique (122, 322) est sensible à la lumière rouge, verte et bleue.

8. Système selon la revendication 6, où le deuxième transducteur optique (122, 322) est sensible à la lumière cyan, magenta et jaune.

9. Système selon l'une quelconque des revendications 6 à 8, où le deuxième filtre comprend un miroir dichroïque (114, 309) prévu pour réfléchir la longueur d'onde d'émission et transmettre la longueur d'onde ou les longueurs d'ondes de lumière visible.

10. Système selon l'une quelconque des revendications 6 à 8, où le deuxième filtre comprend un miroir dichroïque prévu pour réfléchir la longueur d'onde ou les longueurs d'ondes de lumière visible et transmettre la longueur d'onde d'émission.

11. Système selon l'une quelconque des revendications 6 à 8, où le deuxième filtre est prévu pour déformer la longueur d'onde de la lumière visible.

12. Système selon l'une quelconque des revendications précédentes, où le dispositif d'imagerie électronique comprend u dispositif à transfert de charge et/ou une caméra vidéo et/ou une caméra à longueur d'onde d'émission.

13. Système selon l'une quelconque des revendications précédentes, comprenant en outre un processeur prévu pour convertir l'image à la longueur d'onde d'émission en une image convertie à une ou plusieurs composantes de lumière visible, et pour combiner l'image convertie avec, ou superposer l'image convertie à l'image en lumière visible pour écran.

14. Système selon la revendication 13, prévu pour enregistrer l'image en lumière visible à la fréquence de trente images par seconde et la longueur d'onde d'émission à la fréquence de quinze images par seconde, et où soit la longueur d'onde d'émission est convertible en trente images par seconde, soit l'image en lumière visible est convertible en quinze images par seconde, pour une combinaison avec, ou une superposition à l'image en lumière visible.

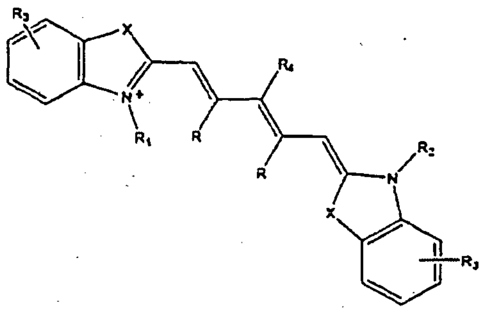
15. Système selon l'une quelconque des revendications précédentes, où la source de lumière d'excitation (104, 304) comprend un laser.

16. Système selon l'une quelconque des revendications précédentes, où la substance fluorescente (110, 310) comprend un ligand de faible poids moléculaire qui s'accumule sur une lésion, le système étant prévu pour visualiser la lésion.

17. Système selon l'une quelconque des revendications précédentes, où la substance fluorescente (110, 310) comprend un colorant fluorescent injectable par injection intraveineuse dans le patient et/ou une substance vaporisable vers le patient.

18. Système selon l'une quelconque des revendications précédentes, où la substance fluorescente (110, 310) comprend au moins un des colorants suivants : vert d'indocyanine ; fluorescéine ; bleu de méthylène et IRDye78-CA.

19. Système selon l'une quelconque des revendications précédentes, où la substance fluorescente (110, 310) est un colorant présentant une structure suivant la formule suivante



où, la valence et la stabilité le permettant,

X représente $C(R)_2$, S, Se, O, ou NR_5 ;
R représente H ou un alkyle inférieur, ou deux occurrences de R, prises ensemble, formant un anneau avec les atomes de carbone par lesquels elles sont reliées ;
R et R_2 représentent, indépendamment, un alkyle inférieur, un alkényle inférieur, un cycloalkyle, un cycloalkylalkyle, un aryle ou un aralkyle, substitué ou non substitué;
R_3 représente, indépendamment pour chaque occurrence, un ou plusieurs substituants sur l'anneau auquel il est attaché ; R_4 représente H, un halogène, ou un éther ou thioéther de phénol ou thiophénol substitué ou non substitué ; et
R_5 représente, indépendamment pour chaque occurrence, un alkyle inférieur, un cycloalkyle, un cycloalkylalkyle, un aryle ou un aralkyle, substitué ou non substitué.

20. Système selon l'une des revendications précédentes, où la source de lumière visible (102, 302) qui éclaire un patient se propage le long d'un premier trajet optique, la source de lumière d'excitation (104, 304) qui éclaire le patient se propage le long d'un deuxième trajet optique, et l'image de la partie du patient se propage vers le dispositif d'imagerie le long d'un troisième trajet optique, au moins deux trajets parmi le premier trajet optique, le deuxième trajet optique et le troisième trajet optique étant coaxiaux.

21. Système selon l'une des revendications, où l'écran (126, 326) comprend un microscope chirurgical.

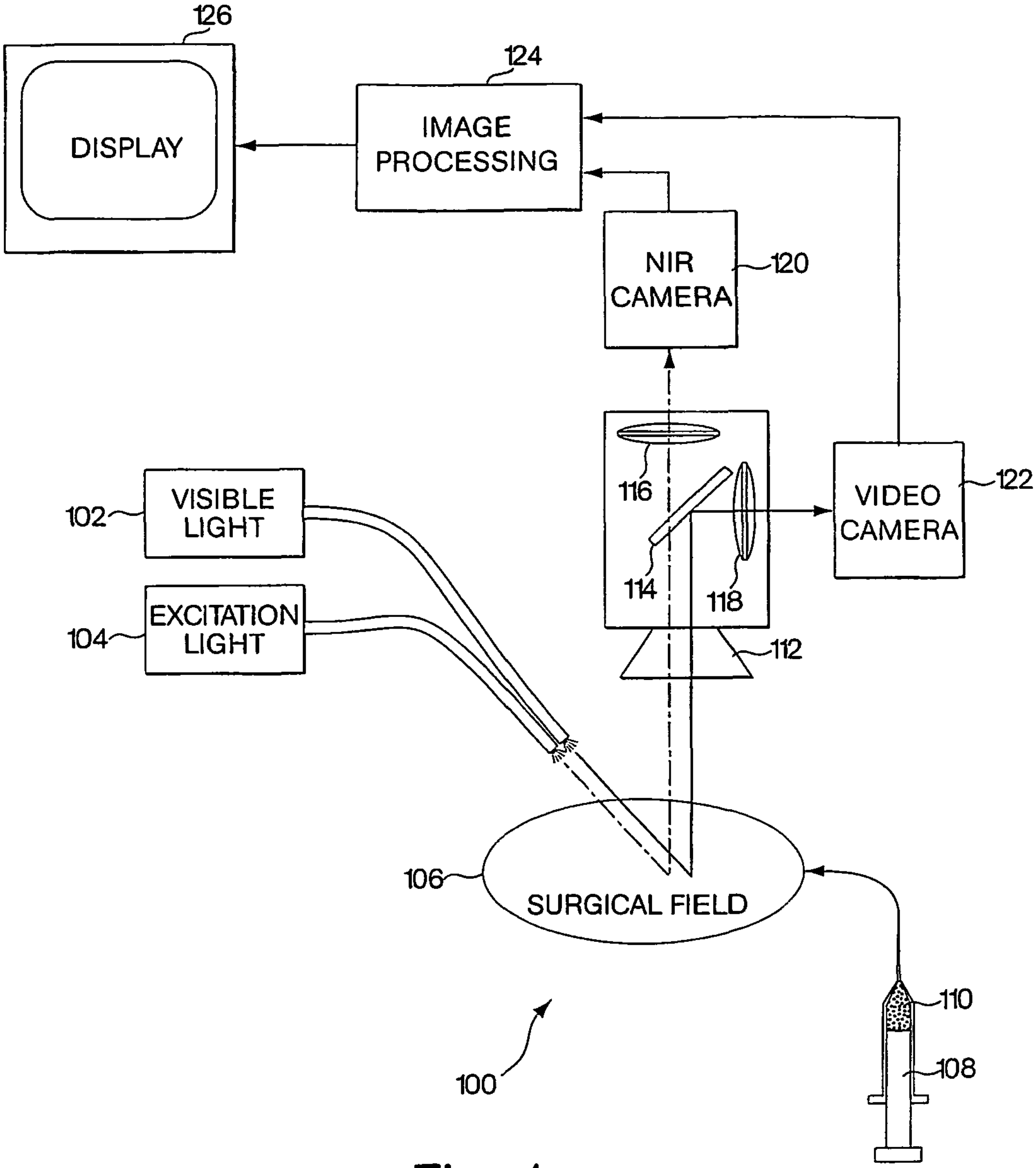

126
DISPLAY
124
IMAGE PROCESSING
NIR CAMERA
120
116
114
118
VIDEO CAMERA
122
102
VISIBLE LIGHT
104
EXCITATION LIGHT
112
106
SURGICAL FIELD
110
108
100

Fig. 1

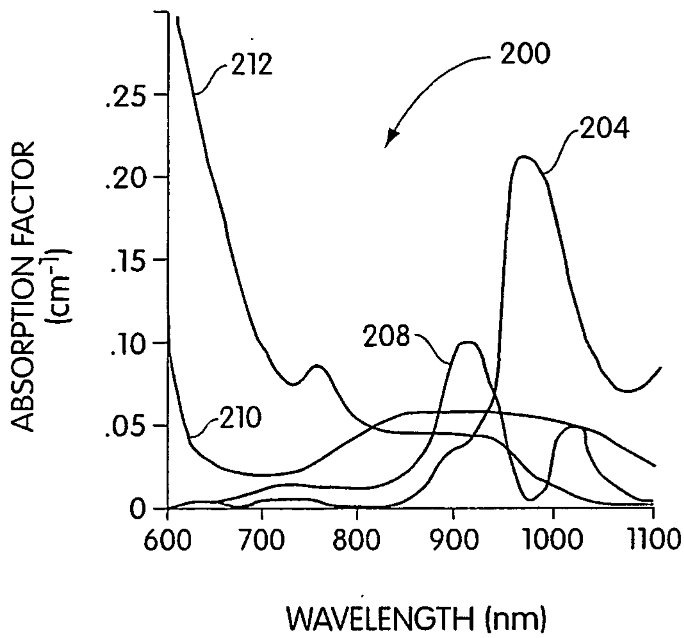

ABSORPTION FACTOR (cm^{-1})
.25
.20
.15
.10
.05
0
600
700
800
900
1000
1100
WAVELENGTH (nm)
200
204
208
210
212

Fig. 2

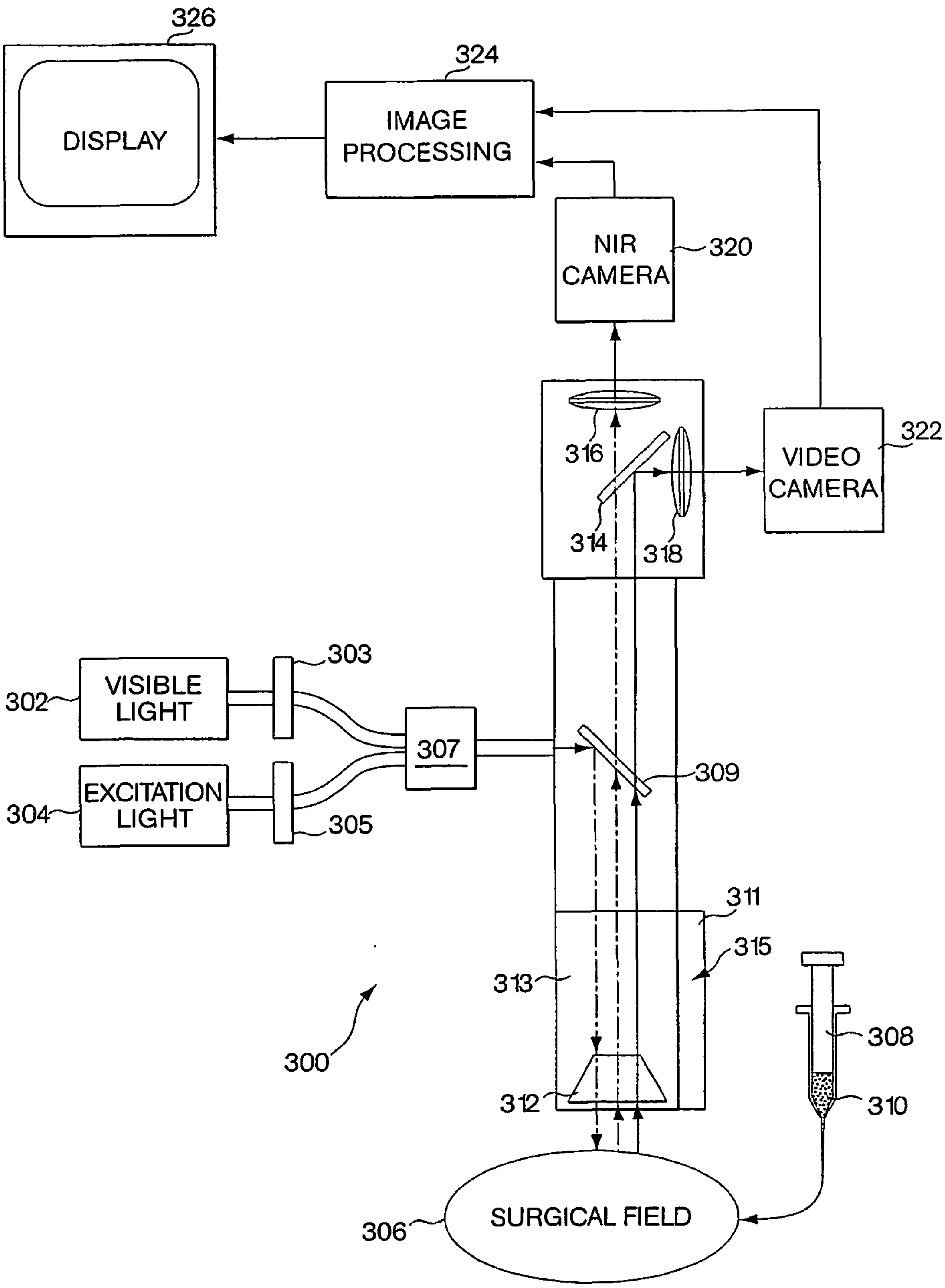

326
DISPLAY
324
IMAGE PROCESSING
NIR CAMERA
320
316
314
318
VIDEO CAMERA
322
303
302
VISIBLE LIGHT
307
309
304
EXCITATION LIGHT
305
311
315
313
308
300
312
310
306
SURGICAL FIELD

Fig. 3

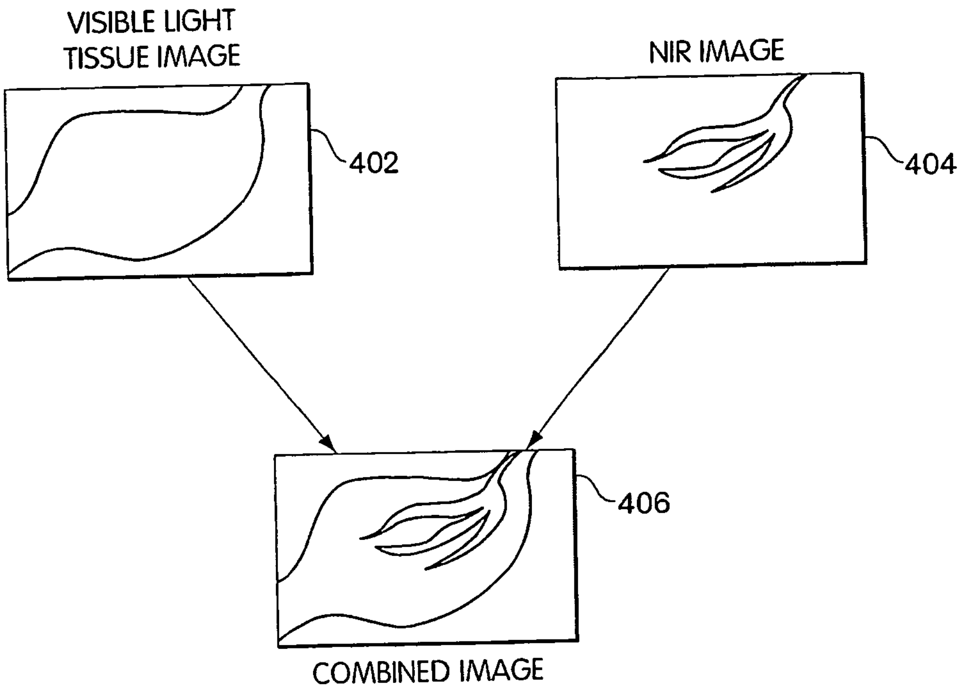

VISIBLE LIGHT
TISSUE IMAGE
402
NIR IMAGE
404
406
COMBINED IMAGE

Fig. 4

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.

Patent documents cited in the description

- US 6293911 B, Imaizumi **[0002]**
- WO 8705297 A, Johnston **[0054]**

Non-patent literature cited in the description

- Periodic Table of the Elements. Handbook of Chemistry and Physics. 1986 **[0061]**

专利名称(译)	医学成像系统		
公开(公告)号	EP1485011B1	公开(公告)日	2013-02-13
申请号	EP2003714102	申请日	2003-03-11
申请(专利权)人(译)	贝斯以色列女执事医疗中心		
当前申请(专利权)人(译)	贝斯以色列女执事医疗中心		
[标]发明人	FRANGIONI JOHN V		
发明人	FRANGIONI, JOHN, V.		
IPC分类号	A61B5/00		
CPC分类号	B82Y5/00 A61B1/00186 A61B1/043 A61B1/045 A61B1/0638 A61B5/0059 A61B5/0071 A61B5/0086 B82Y10/00		
代理机构(译)	法思博事务所		
优先权	60/363413 2002-03-12 US		
其他公开文献	EP1485011A1		
外部链接	Espacenet		

摘要(译)

医学成像系统提供可见光和荧光图像的同时渲染。该系统可以使用小分子形式的染料，其保留在受试者的血流中几分钟，允许对象的循环系统的实时成像叠加在受试者的常规可见光图像上。该系统还可以使用与在诊断重要区域内积累的抗体，抗体片段或配体相关的染料或其他荧光物质。在一个实施例中，该系统提供激发光源以激发荧光物质和可见光源，用于在用于捕获图像的同一光导内进行一般照明。在另一个实施例中，该系统被配置用于通过提供对环境光关闭的操作区域而在开放式外科手术中使用。更广泛地，本文描述的系统可以用于成像应用中，其中可见光图像可以有效地补充由来自荧光物质的荧光发射形成的图像，该荧光物质标记功能感兴趣的区域。