(19)

(11) **EP 1 251 780 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
14.11.2007 Bulletin 2007/46

(21) Application number: **01901819.1**

(22) Date of filing: **05.01.2001**

(51) Int Cl.:
A61B 8/00 *(2006.01)* ***A61K 9/22*** *(2006.01)*
A61K 49/00 *(2006.01)* ***C12Q 1/54*** *(2006.01)*
G01N 33/53 *(2006.01)* ***A61B 5/00*** *(2006.01)*

(86) International application number:
PCT/US2001/000446

(87) International publication number:
WO 2001/052741 (26.07.2001 Gazette 2001/30)

(54) **LUMINESCENT IN VIVO GLUCOSE MEASUREMENT**

LUMINIZENZGLUCOSEMESSUNG

MESURE DE GLUCOSE PAR LUMINESCENCE IN VIVO

(84) Designated Contracting States:
DE FR GB IT

(30) Priority: **21.01.2000 US 489372**

(43) Date of publication of application:
30.10.2002 Bulletin 2002/44

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EP 1 251 780 B1

Printed by Jouve, 75001 PARIS (FR)

Description

BACKGROUND OF THE INVENTION

1. Field of the Invention

[0001] The present invention relates generally to a luminescent *in vivo* glucose measurement, and more particularly to a luminescent *in vivo* glucose measurement using quantum dots.

2. Description of the Background Art

[0002] Measurement of body chemistry components is an essential part of modem health care. By measuring individual body chemistry components of a subject animal or human, such as a subject's blood chemistry, specific health characteristics of the subject can be determined.

[0003] One such body chemistry component is glucose (blood sugar) level. The glucose level in a subject may be analyzed and tracked for a number of reasons, but especially for monitoring diseases such as diabetes. Control of glucose levels in diabetic subjects is know to minimize diabetes side effects and to prolong the life of the subject.

[0004] In the related art, glucose testing and monitoring may be performed in different ways. First, it may be done in vitro (in an artificial environment) by extracting and testing blood specimens. This is undesirable for a variety of reasons, including pain and discomfort, invasiveness, inconvenience, time required, and the provision of an unfortunate avenue for infection.

[0005] The second method is *in vivo* (i.e., in the body) method of glucose measurement. As the name implies, the measurement may be performed through the skin of the subject, and may be non-invasive in nature. This has been done in the related art by illuminating a blood vessel of the subject through the subject's skin and measuring the energy that is absorbed or scattered in the subject's bloodstream. This has advantages of non-invasiveness, quickness, and ease of use. However, it suffers from drawbacks in accuracy, as the results may depend on and be affected by other bloodstream components, blood vessel depth, skin characteristics, etc.

[0006] In another related art blood specimen testing and measurement method, the detection of glucose or blood sugar may be aided by the use of an organic luminescent dye. The related art organic luminescent dye, such as FITC (fluorescein), is capable of covalently bonding to a glucose containing molecule. After the related art luminescent dye has bonded to a glucose analogue which competes with glucose to bind to a substrate, it is illuminated with a light source, causing it to emit photons. The photon emission can be measured and correlated to an amount of glucose present in the sample. Detection and measurement of light emission may therefore yield an emitted light level substantially proportional to the blood sugar level of the subject's blood. Document US.A. 5 001 054 discloses a device for interstitial energy delivery.

[0007] However, related art dyes are organic in nature, and suffer from several drawbacks. First, related art organic luminescent dyes suffer from decomposition, wherein the bond between the dye and the sugar weakens over time. This means that the test or measurement must be taken within a fairly restrictive time window in order to be acceptably accurate. As a result, the related art organic luminescent dye cannot be used for extended periods as is desired for *in vivo* measurements, and is suitable only for *in vitro* laboratory use.

[0008] Second, related art organic luminescent dyes suffer from photo-bleaching, wherein the illuminating light breaks bonds within the dye, resulting in a decrease in luminescence over time. Repeated illumination therefore weakens the luminescent effect.

[0009] A third drawback is that related art organic luminescent dyes have fairly broad emission spectra (i.e., they fluoresce across a relatively broad range of light wavelengths, often overlapping within the excitation wavelength). The emission spectra is a characteristic of the related art organic luminescent dye, and cannot be adjusted to have desired emission and absorption properties. In addition, skin is most transparent to light having a red or near infrared wavelength, but the related art organic luminescent dye produces a bright green luminescence (typically of a wavelength of about 520 nanometers).

[0010] There remains a need in the art, therefore, for an improved *in vivo* blood glucose measurement.

SUMMARY OF THE INVENTION

[0011] A luminescent *in vivo* glucose measurement method for measuring a glucose level in an interstitial fluid of a subject is provided according to a first aspect of the invention. The method comprises the steps of illuminating displaced luminescent molecules with illuminating light, the displaced luminescent molecules and associated captive glucose analogue molecules being contained within an implanted luminescent *in vivo* measurement apparatus implanted within the interstitial fluid of the subject, and measuring an emitted light, the emitted light being emitted in response to the illumination, wherein the emitted light is related to the glucose level in the interstitial fluid.

[0012] A luminescent *in vivo* glucose measurement apparatus for measuring a glucose level in an interstitial fluid of a subject is provided according to a second aspect of the invention. The apparatus comprises a container having an interior region and at least one surface region formed of a semi-permeable membrane that allows glucose to pass through, the container also having an illumination region wherein light may enter the container, an agglutinating layer on at least one interior surface region and apart from the illumination region, a plurality of

captive glucose analogue molecules in the interior region, with a captive sugar of the plurality of captive glucose analogue molecules capable of reversibly attaching to the agglutinating layer, and a plurality of luminescent molecules in the interior region, with a luminescent molecule of the plurality of luminescent molecules being hydrophilic and being bonded to at least one associated captive glucose analogue molecule of the plurality of captive glucose analogue molecules, wherein when a glucose molecule of the subject passes through the at least one surface region formed of a semi-permeable membrane and attaches to the agglutinating layer, a displaced luminescent molecule and an associated captive glucose analogue molecule travels to the illumination region of the container, and wherein illumination of all displaced luminescent molecules and the associated captive glucose analogue molecules through the illumination region produces a luminescence that is related to the glucose level of the interstitial fluid.

[0013] A luminescent *in vivo* glucose measurement compound is provided according to a preferred embodiment of the invention. The compound comprises a quantum dot having a core and a shell, the core selected from the group consisting of indium arsenide, indium nitride, indium phosphide, zinc tellurium, gallium arsenide, gallium antimony, indium antimony, and lead sulfide, and the shell selected from the group consisting of indium phosphide, indium nitride, cadmium sulfide, zinc selenide, zinc sulfide, and lead selenide, at least one captive glucose analogue molecule, and at least one binding molecule that is hydrophilic and is capable of bonding to the at least one captive glucose analogue molecule and to the quantum dot, wherein the quantum dot is capable of absorbing light and emitting light as a result of the absorbing.

[0014] The above and other features and advantages of the present invention will be further understood from the following description of the preferred embodiments thereof, taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015]

FIG. 1 shows detail of one embodiment of the apparatus;

FIG. 2 shows the apparatus when implanted, illustrating the displacing action upon which the glucose measurement is based;

FIG. 3A shows a first embodiment of a luminescent molecule; and

FIG. 3B shows mercaptoacetic acid molecules bonded to a quantum dot.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0016] In one embodiment of a luminescent *in vivo* glucose measurement method of the present invention, the method is used to determine a subject's blood glucose measurement by determining a glucose level present in an interstitial fluid of the subject (the fluid surrounding cells). In a lesser preferred embodiment, the present invention may be used to measure a blood glucose level in a bloodstream of the subject.

[0017] In a first step, an implanted luminescent *in vivo* glucose measurement apparatus is illuminated by a light source. The luminescent *in vivo* glucose measurement apparatus is implanted into the interstitial fluid of the subject and illuminated therein. Although the apparatus may be implanted anywhere on the subject, it is preferred that the apparatus be implanted in an area that is convenient for obtaining a reading. Preferably, the apparatus is implanted in a wrist region of a human subject, and is preferably implanted at a depth of about three to four millimeters below the outer surface of the subject's skin. Although the apparatus may obtain a faster reading when implanted in a blood vessel, clotting or blockage may potentially be encountered. For this reason, implantation in the interstitial fluid is preferred.

[0018] Because the apparatus employs a luminescent material (that may be inorganic), the apparatus may be repeatably used to measure a subject's glucose level. Therefore, the luminescent *in vivo* glucose measurement apparatus is designed to be implanted for a period of at least one to five years.

[0019] Because the apparatus is fairly close to the surface, the illuminating light reaches it. However, not all wavelengths of light are preferred, as the light source should transmit light that travels well through skin. Infrared light (non-visible light having wavelengths in the range of 750 to 2,000 nanometers) is capable of passing through skin with relatively low absorption. Therefore, it is preferred that infrared light be used, and it is further preferred that near infrared light having a wavelength of about 830 nanometers to about 1200 nanometers be used. In a lesser preferred embodiment, visible light may be used to illuminate the implanted apparatus.

[0020] In a second step, as a result of the illumination, the contents of the implanted apparatus emits light. A portion of the emitted light emerges from the skin of the subject and may be detected and measured. The amount of emitted light from the apparatus is related to the amount of glucose in the interstitial fluid. Therefore, the blood glucose level may be reliably and conveniently determined by measuring the interstitial glucose level.

[0021] The glucose level of the interstitial fluid is related to the glucose level of the subject's bloodstream, although there is a short time interval before changes in a blood glucose level are reflected in the interstitial glucose level. The emitted light output may be proportional to the glucose level, although the emitted light level may need

to be adjusted or correlated by use of a table, a constant (s), or a calibration function in order to accurately quantify the glucose level. Alternatively, a fluorescent reference dye may be used. The reference dye is included in the apparatus and always fluoresces when illuminated. The reference dye therefore provides an expected light emission level that can be used to calibrate the measurement by compensating for the implant depth of the apparatus.

[0022] The emitted light may be of the same wavelength as the illuminating light, but is preferably of a separate and distinct wavelength so that a detection device may easily discriminate between the illuminating light and the emitted light, and so that the detection device may easily eliminate any illuminating light that was reflected or scattered. In a preferred embodiment, the emitted light is red shifted by at least 30 nanometers from the illuminating light, allowing use of filters to reject any "background noise" light.

[0023] In addition, the illumination and detection steps are preferably done simultaneously. Because the emitted light has a wavelength (or wavelength band) that is distinct from the wavelength (or wavelength band) of the illuminating light, the emitted light can be detected and measured while the illuminating is being done. The advantage of this is that no wait period is needed between illumination and detection, eliminating the need for precise and expensive time measurement and synchronization equipment. Based on the quantity of emitted light, a detecting device may determine the interstitial glucose level and therefore the blood glucose level.

[0024] FIG. 1 shows detail of one embodiment of a luminescent *in vivo* glucose measurement apparatus. The apparatus includes a container 103 having an inner region 104, an agglutinating layer 109, and luminescent molecules 120 and associated captive glucose analogue molecules 129. The inner region 104 may be filled with the luminescent molecules 120 and associated captive glucose analogue molecules 129 and a solvent or carrier liquid, such as, for example, water or interstitial fluid. Alternatively, the luminescent molecules 120 may be in a colloidal form.

[0025] The shape and physical dimensions of the container 103 may vary as desired. In the present embodiment the container 103 is a cylinder of a diameter less than about one millimeter, or a disk less than about four millimeters in diameter. A small container 103 greatly eases the task of implanting the device and makes it less noticeable to the subject.

[0026] The illumination region 112 is a light transparent region and is only a partial region of the container 103. The illumination region 112 allows light to enter and leave the container 103.

[0027] The agglutinating layer 109 is formed on at least one interior surface region of the container 103, and may cover regions of various sizes, as desired. The agglutinating layer 109 is formed apart from the illumination region 112, so that when the apparatus is illuminated, the illuminating light "I" does not impinge on the agglutinating layer 109.

[0028] The material of the agglutinating layer 109 has an affinity for sugar molecules. In the preferred embodiment, the agglutinating layer 109 is lectin and more preferably is concanavalin A. Because of the sugar affinity of the agglutinating layer 109, any sugar molecules within the inner region 104 tend to attach to the agglutinating layer 109 through a reversible competitive bonding, although they can also detach. Reversible competitive bonding means that a sugar molecule may bond to the agglutinating layer 109 and then detach on its own, with multiple sugar molecules competing for locations at which to bond. Statistically, sugar molecules within the inner region 104 tend to be attached to the agglutinating layer 109 as opposed to drifting in the inner region 104.

[0029] Captive glucose analogue molecules 129 are included in the apparatus as sugar analogues that have the same basic properties as glucose. However, the captive glucose analogue molecules 129 cannot escape the container 103. Captive glucose analogue molecules 129 are contemplated to be sugar analogues such as polysaccharides having glucose units. Dextran is one such sugar analogue consisting of D-glucose linked α-glycosidically, primarily in 1,6 bonds, but with some 1,3 and 1,4. The choice of a sugar analogue is mainly determined by molecular weight, as discussed below.

[0030] The container 103 must have at least one semi-permeable membrane region 105 that allows a subject's glucose to pass through into the inner region 104. The semi-permeable membrane 105 may be a small portion of the container 103, or alternatively the entire container 103 may be formed of the semi-permeable membrane region 105, such as, for example, a dialysis tube. The openings in the semi-permeable membrane region 105 are such that the subject's glucose can pass through the semi-permeable membrane region 105 and into the container 103, but the captive glucose analogue molecules 129 within the apparatus cannot escape. For this reason, dextran is a preferred captive glucose analogue molecule 129, having a molecular weight of 70,000 daltons, as opposed to a molecular weight cut-off characteristic of a typical dialysis tube of about 10,000 daltons.

[0031] The luminescent molecules 120 (discussed in detail below in conjunction with FIGS. 3A and 3B) are present in the inner region 104 for the sole purpose of being displaced by glucose of the subject. When implanted and when no glucose of the subject is present, the quantity of luminescent molecules 120 and associated captive glucose analogue molecules 129 is adequate to substantially attach to and cover the agglutinating layer 109 without a substantial excess.

[0032] It should be noted that not all of the luminescent molecules 120 and associated captive glucose analogue molecules 129 may be attached to the agglutinating layer 109 at any given time. Captive glucose analogue molecules 129 may attach and detach repeatedly, and a small quantity may be drifting freely at any time. These free captive glucose analogue molecules 129 and associated

luminescent molecules 120 may appear as "background noise" when the container 103 is illuminated. This background noise is expected and may be compensated for in the measurement process.

[0033] FIG. 2 shows the apparatus when implanted, illustrating the displacing action upon which the glucose measurement is based. When a subject's glucose 205 enters the inner region 104 by passing through the semipermeable membrane region 105, the subject's glucose 205 may stick to the agglutinating layer 109. Correspondingly, a proportional amount of luminescent molecules 120 and associated captive glucose analogue molecules 129 are displaced from the agglutinating layer 109 to drift in the inner region 104. Illuminating light "I" may enter the inner region 104 through the illumination region 112 and may therefore impinge on displaced luminescent molecules 120 and associated captive glucose analogue molecules 129. As a result, the drifting luminescent molecules 120 may be induced to emit light, with emitted light "E" leaving the apparatus through the illumination region 112 or other appropriate region. The amount of emitted light "E" from the displaced luminescent molecules 120 may then be detected and measured.

[0034] FIG. 3A shows a first embodiment of the luminescent molecule 120. The luminescent molecule 120 includes a quantum dot 300, a hydrophilic coating 308, and may include at least one bi-functional linker molecule 310, depending on the characteristics of the hydrophilic coating 308. The hydrophilic coating 308 may also serve as the bi-functional linker molecule 310. The bi-functional linker molecule 310 may be used to bond a sugar to the hydrophilic coating 308 (which is in turn bonded to the quantum dot 300).

[0035] The quantum dot 300 is formed of inorganic compounds, as opposed to related art luminescent dyes, which are generally organic in nature and tend over time to weaken, decompose, or break free from target molecules. The quantum dot 300 is formed of two or more layers of semiconductor or metallic elements, with the luminescent property of the quantum dot 300 arising from quantum-size confinement due to an extremely small size. Each quantum dot 300 preferably has a diameter in the 5 to 80 nanometer range.

[0036] The characteristics of a quantum dot 300 may be determined by both the physical size and the elemental composition of the quantum dot portion of the luminescent molecule 120. This allows the light absorption characteristic and the luminescent light emission characteristic to be tuned to a narrow wavelength band. For example, in the preferred embodiment, the quantum dot 300 may absorb light of about 830 nanometers and may luminescently emit light at about 900 nanometers.

[0037] The quantum dot 300 has a core 302 and a shell 306. Examples of compounds for use in the core 302 are indium arsenide, indium nitride, indium phosphide, zinc tellurium, gallium arsenide, gallium antimony, indium antimony, and lead sulfide.

[0038] Examples of compounds for use in the shell 306 are indium phosphide, indium nitride, cadmium sulfide, zinc selenide, zinc sulfide, and lead selenide.

[0039] Examples of quantum dot composition are an indium arsenide core and an indium phosphide shell, an indium arsenide core and a cadmium sulfide shell, an indium arsenide cor and a zinc selenide shell, and a lead sulfide core and a lead selenide shell. Of course, other compositions and combinations may be used so long as they have suitable light absorption and emission properties.

[0040] Because of the metallic/semiconductor composition of the quantum dot 300, it is not water soluble. In order to overcome this drawback, the quantum dot 300 is preferably given an organic or inorganic hydrophilic coating 308. For instance, surfactants or lipid bilayers are examples of a class of organic compounds that will make the quantum dot hydrophilic, and silica (SiO_2) is an example of an inorganic material that will make the quantum dot hydrophilic. The hydrophilic coating 308 is preferably a silicon dioxide or hydrophilic organic layer plus a bi-functional linker molecule 310. The hydrophilic organic layer may also serve as the bi-functional linker molecule 310. Examples of the bi-functional linker molecule 310 include but are not limited to thiols, mercaptocarboxylic acids (such as mercaptoacetic acid, for example)or cyanides. The bi-functional linker molecule 310 bonds to an individual captive sugar 129 (see FIG. 1) and also to the hydrophilic coating 308.

[0041] FIG. 3B shows the use of a mercaptoacetic acid 344 as a quantum dot coating, wherein multiple mercaptoacetic acid molecules 344 may bind to the quantum dot 300. When using mercaptoacetic acid 344 as the hydrophilic layer 308, a bi-functional linker molecule 310 is not needed. This is because, as shown by the bonded mercaptoacetic acid molecule 355, the mercapto group attaches to the quantum dot 300, while the acetic acid group binds to the captive sugar 129. The bond to the sugar may be an amide bond, such as shown in FIG. 3B, or may be an ester bond.

[0042] While the invention has been described in detail above, the invention is not intended to be limited to the specific embodiments as described. It is evident that those skilled in the art may now make numerous uses and modifications of and departures from the specific embodiments described herein without departing from the inventive concepts.

Claims

1. A luminescent *in vivo* glucose measurement method for measuring a glucose level in an interstitial fluid of a subject, comprising the steps of:

    illuminating displaced luminescent molecules with illuminating light, said displaced luminescent molecules and associated captive glucose analogue molecules being contained within an

implanted luminescent *in vivo* measurement apparatus implanted within said interstitial fluid of said subject; and
measuring an emitted light, said emitted light being emitted in response to said illumination;
wherein said emitted light is related to said glucose level in said interstitial fluid.

2. The luminescent *in vivo* glucose measurement method of claim 1, wherein said glucose level in said interstitial fluid is substantially equal to a blood glucose level.

3. The luminescent *in vivo* glucose measurement method of claim 1, wherein said method is used to measure a glucose level in a bloodstream of said subject.

4. The luminescent *in vivo* glucose measurement method of claim 1, wherein said displaced luminescent molecules are inorganic.

5. The luminescent *in vivo* glucose measurement method of claim 1, wherein said emitted light is correlated to a interstitial glucose level.

6. The luminescent *in vivo* glucose measurement method of claim 1, wherein said luminescent *in vivo* measurement apparatus has been implanted about three to about four millimeters below an outer surface of a patient's skin.

7. The luminescent *in vivo* glucose measurement method of claim 1, wherein said illuminating light is of a first wavelength and said emitted light is of a second wavelength.

8. The luminescent *in vivo* glucose measurement method of claim 1, wherein said illuminating light is an infrared light.

9. The luminescent *in vivo* glucose measurement method of claim 1, wherein a wavelength of said illuminating light is in a range of about 800 nanometers to about 2000 nanometers.

10. The luminescent *in vivo* glucose measurement method of claim 1, wherein a wavelength of said illuminating light is about 830 nanometers and a wavelength of said emitted light is about 900 nanometers.

11. The luminescent *in vivo* glucose measurement method of claim 1, wherein said illuminating light travels from outside said subject, through said subject's skin, and into said luminescent *in vivo* measurement apparatus.

12. The luminescent *in vivo* glucose measurement method of claim 1, wherein said emitted light travels from said luminescent *in vivo* measurement apparatus, through said subject's skin, and to a region outside said subject.

13. The luminescent *in vivo* glucose measurement method of claim 1, wherein said luminescent *in vivo* measurement apparatus further comprises:

a container having an interior region and at least one surface region formed of a semi-permeable membrane that allows glucose to pass through, said container also having an illumination region wherein light may enter said container;
an agglutinating layer on at least one interior surface region and apart from said illumination region;
a plurality of captive glucose analogue molecules in said interior region, with a captive glucose analogue molecule of said plurality of captive glucose analogue molecules capable of reversibly attaching to said agglutinating layer; and
a plurality of luminescent molecules in said interior region, with a luminescent molecule of said plurality of luminescent molecules being hydrophilic and being bonded to at least one associated captive glucose analogue molecule of said plurality of captive glucose analogue molecules;
wherein when a glucose molecule of said subject passes through said at least one surface region formed of a semi-permeable membrane and attaches to said agglutinating layer, a displaced luminescent molecule and an associated captive glucose analogue molecule is displaced and travels to said illumination region of said container, and wherein illumination of all displaced luminescent molecules and said associated captive glucose analogue molecules through said illumination region produces a luminescence that is related to said glucose level of said interstitial fluid.

14. The luminescent *in vivo* glucose measurement method of claim 13, wherein said plurality of luminescent molecules is inorganic.

15. The luminescent *in vivo* glucose measurement method of claim 13, wherein said glucose level in said interstitial fluid is substantially equal to a blood glucose level.

16. The luminescent *in vivo* glucose measurement method of claim 13, wherein said container is a dialysis tube.

17. The luminescent *in vivo* glucose measurement method of claim 14, wherein an inorganic luminescent molecule of said plurality of inorganic luminescent molecules further comprises:

a quantum dot having a core and a shell, said core selected from the group consisting of indium arsenide, indium nitride, indium phosphide, zinc tellurium, gallium arsenide, gallium antimony, indium antimony, and lead sulfide, and said shell selected from the group consisting of indium phosphide, indium nitride, cadmium sulfide, zinc selenide, zinc sulfide, and lead selenide;
at least one captive glucose analogue molecule; and
at least one binding molecule selected from the group consisting of silicon dioxide, mercaptocarboxylic acids, cyanides, and thiols, said at least one binding molecule being hydrophilic and being capable of bonding to said at least one captive glucose analogue molecule and to said quantum dot.

18. The luminescent *in vivo* glucose measurement method of claim 17, wherein said inorganic luminescent molecule further includes a hydrophilic outer shell surrounding said shell of said quantum dot and to which said at least one binding molecule attaches.

19. The luminescent *in vivo* glucose measurement method of claim 18, wherein said hydrophilic outer shell is organic.

20. The luminescent *in vivo* glucose measurement method of claim 19, wherein said hydrophilic outer shell is selected from the group consisting of mercaptocarboxylic acids, cyanides, thiols, surfactants, and lipid bilayers.

21. The luminescent *in vivo* glucose measurement method of claim 18, wherein said hydrophilic outer shell is inorganic.

22. The luminescent *in vivo* glucose measurement method of claim 21, wherein said hydrophilic outer shell is selected from the group consisting of silicon dioxide, silicon nitride, silicon oxynitride, and silicon oxyhydride.

23. The luminescent *in vivo* glucose measurement method of claim 13, wherein said agglutinating layer has an affinity for glucose and sugar analogues.

24. The luminescent *in vivo* glucose measurement method of claim 13, wherein said agglutinating layer is lectin.

25. The luminescent *in vivo* glucose measurement method of claim 13, wherein said agglutinating layer is concanavalin A.

26. The luminescent *in vivo* glucose measurement method of claim 13, wherein said plurality of captive glucose analogue molecules is a polysaccharide.

27. The luminescent *in vivo* glucose measurement method of claim 13, wherein said plurality of captive glucose analogue molecules is dextran.

28. A luminescent *in vivo* glucose measurement apparatus for measuring a glucose level in an interstitial fluid of a subject, comprising:

a container having an interior region and at least one surface region formed of a semi-permeable membrane that allows glucose to pass through, said container also having an illumination region wherein light may enter said container;
an agglutinating layer on at least one interior surface region and apart from said illumination region;
a plurality of captive glucose analogue molecules in said interior region, with a captive sugar of said plurality of captive glucose analogue molecules capable of reversibly attaching to said agglutinating layer; and
a plurality of luminescent molecules in said interior region, with a luminescent molecule of said plurality of luminescent molecules being hydrophilic and being bonded to at least one associated captive glucose analogue molecule of said plurality of captive glucose analogue molecules;
wherein when a glucose molecule of said subject passes through said at least one surface region formed of a semi-permeable membrane and attaches to said agglutinating layer, a displaced luminescent molecule and an associated captive glucose analogue molecule travels to said illumination region of said container, and wherein illumination of all displaced luminescent molecules and said associated captive glucose analogue molecules through said illumination region
produces a luminescence that is related to said glucose level of said interstitial fluid.

29. The luminescent *in vivo* glucose measurement apparatus of claim 28, wherein said glucose level in said interstitial fluid is substantially equal to a blood glucose level.

30. The luminescent *in vivo* glucose measurement apparatus of claim 28, wherein said apparatus is implanted in a bloodstream of said subject.

31. The luminescent *in vivo* glucose measurement apparatus of claim 28, wherein said plurality of luminescent molecules is inorganic.

32. The luminescent *in vivo* glucose measurement apparatus of claim 28, wherein said container is a dialysis tube.

33. The luminescent *in vivo* glucose measurement apparatus of claim 31, wherein a luminescent molecule of said plurality of luminescent molecules further comprises:

a quantum dot having a core and a shell, said core selected from the group consisting of indium arsenide, indium nitride, indium phosphide, zinc tellurium, gallium arsenide, gallium antimony, indium antimony, and lead sulfide, and said shell selected from the group consisting of indium phosphide, indium nitride, cadmium sulfide, zinc selenide, zinc sulfide, and lead selenide;
at least one captive glucose analogue molecule; and
at least one binding molecule that is hydrophilic and that is capable of bonding to said at least one captive glucose analogue molecule and to said quantum dot.

34. The luminescent *in vivo* glucose measurement apparatus of claim 33, wherein said at least one binding molecule is selected from the group consisting of mercaptocarboxylic acids, cyanides, and thiols.

35. The luminescent *in vivo* glucose measurement apparatus of claim 33, wherein said inorganic luminescent molecule further includes a hydrophilic outer shell surrounding said shell of said quantum dot and to which said at least one binding molecule attaches.

36. The luminescent *in vivo* glucose measurement apparatus of claim 35, wherein said hydrophilic outer shell is organic.

37. The luminescent *in vivo* glucose measurement apparatus of claim 36, wherein said hydrophilic outer shell is selected from the group consisting of mercaptocarboxylic acids, cyanides, thiols, surfactants, and lipid bilayers.

38. The luminescent *in vivo* glucose measurement apparatus of claim 35, wherein said hydrophilic outer shell is inorganic.

39. The luminescent *in vivo* glucose measurement apparatus of claim 38, wherein said hydrophilic outer shell is selected from the group consisting of silicon dioxide, silicon nitride, silicon oxynitride, and silicon oxyhydride.

40. The luminescent *in vivo* glucose measurement apparatus of claim 28, wherein said agglutinating layer has an affinity for glucose and sugar analogues.

41. The luminescent *in vivo* glucose measurement apparatus of claim 28, wherein said agglutinating layer is lectin.

42. The luminescent *in vivo* glucose measurement apparatus of claim 28, wherein said agglutinating layer is concanavalin A.

43. The luminescent *in vivo* glucose measurement apparatus of claim 28, wherein said captive glucose analogue molecules is a polysaccharide.

44. The luminescent *in vivo* glucose measurement apparatus of claim 28, wherein said plurality of captive glucose analogue molecules is dextran.

Patentansprüche

1. In vivo-Lumineszenzglucosemeßverfahren zur Messung eines Glucosegehalts in einem interstitiellen Fluid einer Testperson, welches die Schritte umfaßt:

Bestrahlen verdrängter Lumineszenzmoleküle mit Bestrahlungslicht, wobei die verdrängten Lumineszenzmoleküle und assoziierte eingefangene Glucoseanalogmoleküle innerhalb einer implantierten in vivo-Lumineszenzmeßvorrichtung enthalten sind, die innerhalb des interstitiellen Fluids der Testperson implantiert ist; und
Messen eines emittierten Lichts, wobei das emittierte Licht in Ansprechung auf die Bestrahlung emittiert wird;
wobei das emittierte Licht in Beziehung gesetzt wird zum Glucosegehalt in dem interstitiellen Fluid.

2. In vivo-Lumineszenzglucosemeßverfahren nach Anspruch 1, wobei der Glucosegehalt im interstitiellen Fluid im wesentlichen gleich zu einem Blutglucosegehalt ist.

3. In vivo-Lumineszenzglucosemeßverfahren nach Anspruch 1, wobei das Verfahren verwendet wird, um einen Glucosegehalt in einem Blutstrom der Testperson zu messen.

4. In vivo-Lumineszenzglucosemeßverfahren nach Anspruch 1, wobei die verdrängten Lumineszenzmoleküle anorganisch sind.

5. In vivo-Lumineszenzglucosemeßverfahren nach Anspruch 1, wobei das emittierte Licht mit einem interstitiellen Glucosegehalt korreliert wird.

6. In vivo-Lumineszglucosemeßverfahren nach Anspruch 1, wobei die in vivo-Lumineszmeßvorrichtung etwa 3 bis etwa 4 mm unterhalb einer äußeren Oberfläche der Haut des Patienten implantiert worden ist.

7. In vivo-Lumineszglucosemeßverfahren nach Anspruch 1, wobei das Bestrahlungslicht von einer ersten Wellenlänge und das emittierte Licht von einer zweiten Wellenlänge ist.

8. In vivo-Lumineszenzglucosemeßverfahren nach Anspruch 1, wobei das Bestrahlungslicht ein Infrarotlicht ist.

9. In vivo-Lumineszenzglucosemeßverfahren nach Anspruch 1, wobei eine Wellenlänge des Bestrahlungslichts innerhalb eines Bereichs von etwa 800 Nanometern bis etwa 2000 Nanometern ist.

10. In vivo-Lumineszenzglucosemeßverfahren nach Anspruch 1, wobei eine Wellenlänge des Bestrahlungslichts etwa 830 Nanometer und eine Wellenlänge des emittierten Lichts etwa 900 Nanometer ist.

11. In vivo-Lumineszenzglucosemeßverfahren nach Anspruch 1, wobei das Bestrahlungslicht von außerhalb der Testperson, durch die Haut der Testperson und in die in vivo-Lumineszenzmeßvorrichtung gelangt.

12. In vivo-Lumineszenzglucosemeßverfahren nach Anspruch 1, wobei das emittierte Licht aus der in vivo-Lumineszenzmeßvorrichtung, durch die Haut der Testperson und zu einem Bereich außerhalb der Testperson gelangt.

13. In vivo-Lumineszenzglucosemeßverfahren nach Anspruch 1, wobei die in vivo-Lumineszenzmeßvorrichtung weiter umfaßt:

einen Behälter mit einem inneren Bereich und wenigsten einem Oberflächenbereich, der aus einer halbpermeablen Membran gebildet ist, die erlaubt, daß Glucose hindurchgelangt, wobei der Behälter ebenfalls einen Bestrahlungsbereich aufweist, bei dem Licht in den Behälter eintreten kann;
eine Agglutinierungsschicht auf wenigstens einem inneren Oberflächenbereich und entfernt von dem Bestrahlungsbereich;
eine Vielzahl von eingefangenen Glucoseanalogmolekülen im inneren Bereich, wobei eingefangenes Glucoseanalogmolekül der Vielzahl der eingefangenen Glucoseanalogmoleküle in der Lage ist, sich reversibel an der Agglutinierungsschicht anzufügen; und
eine Vielzahl von Lumineszenzmolekülen im inneren Bereich, wobei ein Lumineszenzmolekül der Vielzahl der Lumineszenzmoleküle hydrophil ist und an wenigstens ein assoziiertes eingefangenes Glucoseanalogmolekül der Vielzahl der eingefangenen Glucoseanalogmoleküle angebunden ist;
wobei, wenn ein Glucosemolekül der Testperson durch wenigstens einen Oberflächenbereich gelangt, der aus einer halbpermeablen Membran gebildet ist, und sich an der Agglutinierungsschicht anfügt, ein verdrängtes Lumineszenzmolekül und ein assoziiertes eingefangenes Glucoseanalogmolekül verdrängt werden und zum Bestrahlungsbereich des Behälters gelangen, und wobei eine Bestrahlung aller verdrängten Lumineszenzmoleküle und der assoziierten eingefangenen Glucoseanalogmoleküle durch den Bestrahlungsbereich eine Lumineszenz erzeugt, die mit dem Glucosegehalt des interstitiellen Fluids in Beziehung gesetzt wird.

14. In vivo-Lumineszenzglucosemeßverfahren nach Anspruch 13, wobei die Vielzahl der Lumineszenzmoleküle anorganisch ist.

15. In vivo-Lumineszenzglucosemeßverfahren nach Anspruch 13, wobei der Glucosegehalt im interstitiellen Fluid im wesentlichen gleich zu einem Blutglucosegehalt ist.

16. In vivo-Lumineszenzglucosemeßverfahren nach Anspruch 13, wobei der Behälter ein Dialyseröhrchen ist.

17. In vivo-Lumineszenzglucosemeßverfahren nach Anspruch 14, wobei ein anorganisches Lumineszenzmolekül der Vielzahl der anorganischen Lumineszenzmoleküle weiter umfaßt:

einen Quantenpunkt mit einem Kern und einer Schale, wobei der Kern ausgewählt wird aus der Gruppe bestehend aus Indiumarsenid, Indiumnitrid, Indiumphosphid, Zinktellur, Galliumarsenid, Galliumantimon, Indiumantimon und Bleisulfid, und wobei die Schale ausgewählt wird aus der Gruppe bestehend aus Indiumphosphid, Indiumnitrid, Kadmiumsulfid, Zinkselenid, Zinksulfid und Bleiselenid;
wenigstens ein eingefangenes Glucoseanalogmolekül; und
wenigstens ein Bindungsmolekül, das ausgewählt wird aus der Gruppe bestehend aus Siliciumdioxid, Mercaptocarbonsäuren, Cyaniden und Thiolen, wobei wenigstens ein Bindungsmolekül hydrophil ist und in der Lage ist, sich an wenigstens ein eingefangenes Glucoseanalogmolekül und an den Quantenpunkt anzubinden.

18. In vivo-Lumineszenzglucosemeßverfahren nach Anspruch 17, wobei das anorganische Lumineszenzmolekül ferner eine hydrophile äußere Schale einschließt, die den Kern des Quantenpunkts umgibt, und an das sich wenigstens eine Bindungsmolekül anfügt.

19. In vivo-Lumineszenzglucosemeßverfahren nach Anspruch 18, wobei die hydrophile äußere Schale organisch ist.

20. In vivo-Lumineszenzglucosemeßverfahren nach Anspruch 19, wobei die hydrophile äußere Schale ausgewählt wird aus der Gruppe bestehend aus Mercaptocarbonsäuren, Cyaniden, Thiolen, oberflächenaktiven Mitteln und Lipiddoppelschichten.

21. In vivo-Lumineszenzglucosemeßverfahren nach Anspruch 18, wobei die hydrophile äußere Schale anorganisch ist.

22. In vivo-Lumineszglucosemeßverfahren nach Anspruch 21, wobei die hydrophile äußere Schale ausgewählt wird aus der Gruppe bestehend aus Siliciumdioxid, Siliciumnitrid, Siliciumoxynitrid und Siliciumoxyhydrid.

23. In vivo-Lumineszenzglucosemeßverfahren nach Anspruch 13, wobei die Agglutinierungsschicht eine Affinität für Glucose und Zuckeranaloga aufweist.

24. In vivo-Lumineszenzglucosemeßverfahren nach Anspruch 13, wobei die Agglutinierungsschicht Lectin ist.

25. In vivo-Lumineszenzglucosemeßverfahren nach Anspruch 13, wobei die Agglutinierungsschicht Concanavalin A ist.

26. In vivo-Lumineszenzglucosemeßverfahren nach Anspruch 13, wobei die Vielzahl an eingefangenen Glucoseanalogmolekülen ein Polysaccharid ist.

27. In vivo-Lumineszenzglucosemeßverfahren nach Anspruch 13, wobei die Vielzahl an eingefangenen Glucoseanalogmolekülen Dextran ist.

28. In vivo-Lumineszenzglucosemeßvorrichtung zum Messen eines Glucosegehalts in einem interstitiellen Fluid einer Testperson, welche umfaßt:

einen Behälter mit einem inneren Bereich und wenigstens einem Oberflächenbereich, der aus einer halbpermeablen Membran gebildet ist, die erlaubt, daß Glucose hindurchgelangt, wobei der Behälter ebenfalls einen Bestrahlungsbereich aufweist, bei dem Licht in den Behälter eintreten kann;

eine Agglutinierungsschicht auf wenigstens einem inneren Oberflächenbereich und entfernt vom Bestrahlungsbereich;

eine Vielzahl von eingefangenen Glucoseanalogmolekülen im inneren Bereich, wobei ein eingefangener Zucker der Vielzahl der eingefangenen Glucoseanalogmoleküle in der Lage ist, sich reversibel an der Agglutinierungsschicht anzufügen; und

eine Vielzahl von Lumineszenzmolekülen im inneren Bereich, wobei ein Lumineszenzmolekül der Vielzahl der Lumineszenzmoleküle hydrophil ist und an wenigstens ein assoziiertes eingefangenes Glucoseanalogmolekül der Vielzahl der eingefangenen Glucoseanalogmoleküle angebunden ist;

wobei, wenn ein Glucosemolekül der Testperson durch wenigstens einen Oberflächenbereich, der aus einer semipermeablen Membran gebildet ist, gelangt und sich an der Agglutinierungsschicht anfügt, ein verdrängtes Lumineszenzmolekül und ein assoziiertes eingefangenes Glucoseanalogmolekül zum Bestrahlungsbereich des Behälters gelangen, und wobei eine Bestrahlung aller verdrängten Lumineszenzmoleküle und der assoziierten eingefangenen Glucoseanalogmoleküle durch den Bestrahlungsbereich eine Lumineszenz erzeugt, die mit dem Glucosegehalt des interstitiellen Fluids in Beziehung gesetzt wird.

29. In vivo-Lumineszenzglucosemeßvorrichtung nach Anspruch 28, wobei der Glucosegehalt im interstitiellen Fluid im wesentlichen gleich zu einem Blutglucosegehalt ist.

30. In vivo-Lumineszenglucosemeßvorrichtung nach Anspruch 28, wobei die Vorrichtung in einem Blutstrom der Testperson implantiert ist.

31. In vivo-Lumineszenzglucosemeßvorrichtung nach Anspruch 28, wobei die Vielzahl der Lumineszenzmoleküle anorganisch ist.

32. In vivo-Lumineszenzglucosemeßvorrichtung nach Anspruch 28, wobei der Behälter ein Dialyseröhrchen ist.

33. In vivo-Lumineszenzglucosemeßvorrichtung nach Anspruch 31, wobei ein Lumineszenzmolekül der Vielzahl der Lumineszenzmoleküle ferner umfaßt:

einen Quantenpunkt mit einem Kern und einer Schale, wobei der Kern ausgewählt ist aus der Gruppe bestehend aus Indiumarsenid, Indiumnitrid, Indiumphosphid, Zinktellur, Galliumarsenid, Galliumantimon, Indiumantimon und Bleisulfid, und wobei die Schale ausgewählt

wird aus der Gruppe bestehend aus Indiumphosphid, Indiumnitrid, Kadmiumsulfid, Zinkselenid, Zinksulfid und Bleiselenid;
wenigstens ein eingefangenes Glucoseanalogmolekül; und
wenigstens ein Bindungsmolekül, das hydrophil ist und das in der Lage ist, sich an das wenigstens eine eingefangene Glucoseanalogmolekül und an den Quantenpunkt anzubinden.

34. In vivo-Lumineszenzglucosemeßvorrichtung nach Anspruch 33, wobei das wenigstens eine Bindungsmolekül ausgewählt ist aus der Gruppe bestehend aus Mercaptocarbonsäuren, Cyaniden und Thiolen.

35. In vivo-Lumineszenzglucosemeßvorrichtung nach Anspruch 33, wobei das anorganische Lumineszenzmolekül ferner eine hydrophile äußere Schale einschließt, die die Schale des Quantenpunkts umgibt, und an die sich das wenigstens eine Bindungsmolekül anfügt.

36. In vivo-Lumineszenzglucosemeßvorrichtung nach Anspruch 35, wobei die hydrophile äußere Schale organisch ist.

37. In vivo-Lumineszenzglucosemeßvorrichtung nach Anspruch 36, wobei die hydrophile äußere Schale ausgewählt ist aus der Gruppe bestehend aus Mercaptocarbonsäuren, Cyaniden, Thiolen, oberflächenaktiven Mitteln und Lipiddoppelschichten.

38. In vivo-Lumineszenglucosemeßvorrichtung nach Anspruch 35, wobei die hydrophile äußere Schale anorganisch ist.

39. In vivo-Lumineszenglucosemeßvorrichtung nach Anspruch 38, wobei die hydrophile äußere Schale ausgewählt ist aus der Gruppe bestehend aus Siliciumdioxid, Siliciumnitrid, Siliciumoxynitrid und Siliciumoxyhydrid.

40. In vivo-Lumineszenzglucosemeßvorrichtung nach Anspruch 28, wobei die Agglutinierungsschicht eine Affinität für Glucose und Zuckeranaloga aufweist.

41. In vivo-Lumineszenzglucosemeßvorrichtung nach Anspruch 28, wobei die Agglutinierungsschicht Lectin ist.

42. In vivo-Lumineszenzglucosemeßvorrichtung nach Anspruch 28, wobei die Agglutinierungsschicht Concanavalin A ist.

43. In vivo-Lumineszenzglucosemeßvorrichtung nach Anspruch 28, wobei die eingefangenen Glucoseanalogmoleküle ein Polysaccharid sind.

44. In vivo-Lumineszenzglucosemeßvorrichtung nach Anspruch 28, wobei die Vielzahl der eingefangenen Glucoseanalogmoleküle Dextran sind.

Revendications

1. Procédé de mesure du glucose *in vivo* par luminescence pour mesurer un taux de glucose dans un fluide interstitiel d'un sujet, comprenant les étapes consistant à :

■ illuminer les molécules luminescentes déplacées avec une lumière illuminante, lesdites molécules luminescentes déplacées et molécules analogues de glucose captif associées étant contenues dans un appareil de mesure *in vivo* par luminescence implanté dans ledit fluide interstitiel dudit sujet ; et
■ mesurer une lumière émise, ladite lumière émise étant émise en réponse à ladite illumination ;

dans lequel ladite lumière émise est liée au dit taux de glucose dans ledit fluide interstitiel.

2. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 1, dans lequel ledit taux de glucose dans ledit fluide interstitiel est sensiblement égal à un taux de glucose sanguin.

3. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 1, dans lequel ledit procédé est utilisé pour mesurer un taux de glucose dans un courant sanguin dudit sujet.

4. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 1, dans lequel lesdites molécules luminescentes déplacées sont inorganiques.

5. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 1, dans lequel ladite lumière émise est corrélée à un taux de glucose interstitiel.

6. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 1, dans lequel ledit appareil de mesure *in vivo* par luminescence a été implanté environ trois à environ quatre millimètres en dessous d'une surface externe de la peau d'un patient.

7. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 1, dans lequel ladite lumière illuminante est d'une première longueur d'ondes et ladite lumière émise est d'une deuxième longueur d'ondes.

8. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 1, dans lequel ladite lumière illuminante est une lumière infrarouge.

9. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 1, dans lequel une longueur d'onde de ladite lumière illuminante est dans une plage d'environ 800 nanomètres à environ 2000 nanomètres.

10. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 1, dans lequel une longueur d'ondes de ladite lumière illuminante est d'environ 830 nanomètres et une longueur d'ondes de ladite lumière émise est d'environ 900 nanomètres.

11. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 1, dans lequel ladite lumière illuminante traverse ledit sujet depuis l'extérieur, en passant à travers la peau dudit sujet, et entre dans ledit appareil de mesure *in vivo* par luminescence.

12. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 1, dans lequel ladite lumière émise part depuis ledit appareil de mesure *in vivo* par luminescence, passe à travers la peau dudit sujet, et arrive dans une région située à l'extérieur dudit sujet.

13. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 1, dans lequel ledit appareil de mesure *in vivo* par luminescence comprend en outre :

■ un conteneur ayant une région intérieure et au moins une région de surface formée d'une membrane semi-perméable qui permet au glucose de passer au travers, ledit conteneur ayant aussi une région d'illumination où la lumière peut entrer dans ledit conteneur ;
■ une couche d'agglutination sur au moins une région de surface intérieure et éloignée de ladite région d'illumination ;
■ une pluralité de molécules analogues de glucose captif dans ladite région intérieure, avec une molécule analogue de glucose captif de ladite pluralité de molécules analogues de glucose captif capable de se lier de manière réversible à ladite couche d'agglutination ; et
■ une pluralité de molécules luminescentes dans ladite région intérieure, avec une molécule luminescente de ladite pluralité de molécules luminescentes qui est hydrophile et liée à au moins une molécule analogue de glucose captif associée de ladite pluralité de molécules analogues de glucose captif ;

où quand une molécule de glucose dudit sujet passe à travers ladite au moins une région de surface formée d'une membrane semi-perméable et se fixe à ladite couche d'agglutination, une molécule luminescente déplacée et une molécule analogue de glucose captif associée sont déplacées et traversent ladite région d'illumination dudit conteneur, et où l'illumination de toutes les molécules luminescentes déplacées et lesdites molécules analogues de glucose captif associées à travers ladite région d'illumination produit une luminescence qui est associée au dit taux de glucose dudit fluide interstitiel.

14. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 13, dans lequel ladite pluralité de molécules luminescentes est inorganique.

15. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 13, dans lequel ledit taux de glucose dans ledit fluide interstitiel est sensiblement égal à un taux de glucose sanguin.

16. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 13, dans lequel ledit conteneur est un tube de dialyse.

17. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 14, dans lequel une molécule luminescente inorganique de ladite pluralité de molécules luminescentes inorganiques comprend en outre :

■ une boîte quantique ayant un coeur et une coque, ledit coeur étant choisi dans le groupe constitué par l'arséniure d'indium, le nitrure d'indium, le phosphure d'indium, le tellure de zinc, l'arséniure de gallium, l'antimoine de gallium, l'antimoine d'indium et le sulfure de plomb, et ladite coque étant choisie dans le groupe constitué par le phosphure d'indium, le nitrure d'indium, le sulfure de cadmium, le séléniure de zinc, le sulfure de zinc, et le séléniure de plomb ;
■ au moins une molécule analogue de glucose captif ; et
■ au moins une molécule de liaison choisie dans le groupe constitué par le dioxyde de silicium, les acides mercaptocarboxyliques, les cyanures, et les thiols, ladite au moins une molécule de liaison étant hydrophile et étant capable de se lier à au moins une molécule analogue de glucose captif et à ladite boîte quantique.

18. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 17, dans lequel ladite molécule luminescente inorganique comprend en outre une coque externe hydrophile entourant ladite coque de ladite boîte quantique et à laquelle ladite

au moins une molécule de liaison se lie.

19. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 18, dans lequel ladite coque externe hydrophile est organique.

20. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 19, dans lequel ladite coque externe hydrophile est choisie dans le groupe constitué par les acides mercaptocarboxyliques, les cyanures, les thiols, les tensioactifs et les bicouches lipidiques.

21. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 18, dans lequel ladite coque externe hydrophile est inorganique.

22. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 21, dans lequel ladite coque externe hydrophile est choisie dans le groupe constitué par le dioxyde de silicium, le nitrure de silicium, l'oxynitrure de silicium et l'oxyhydrure de silicium.

23. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 13, dans lequel ladite couche d'agglutination a une affinité pour le glucose et les analogues de sucre.

24. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 13, dans lequel ladite couche d'agglutination est la lectine.

25. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 13, dans lequel ladite couche d'agglutination est la concanavaline A.

26. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 13, dans lequel ladite pluralité de molécules analogues de glucose captif est un polysaccharide.

27. Procédé de mesure du glucose *in vivo* par luminescence selon la revendication 13, dans lequel ladite pluralité de molécules analogues de glucose captif est le dextrane.

28. Appareil de mesure du glucose *in vivo* par luminescence pour mesurer un taux de glucose dans un fluide interstitiel d'un sujet, comprenant :

- ■ un conteneur ayant une région intérieure et au moins une région de surface formée d'une membrane semi-perméable qui permet au glucose de passer au travers, ledit conteneur ayant aussi une région d'illumination où la lumière peut entrer dans ledit conteneur ;
- ■ une couche d'agglutination sur au moins une région de surface intérieure et éloignée de ladite région d'illumination ;
- ■ une pluralité de molécules analogues de glucose captif dans ladite région intérieure, avec un sucre captif de ladite pluralité de molécules analogues de glucose captif capable de se lier de manière réversible à ladite couche d'agglutination ; et
- ■ une pluralité de molécules luminescentes dans ladite région intérieure, avec une molécule luminescente de ladite pluralité de molécules luminescentes qui est hydrophile et liée à au moins une molécule analogue de glucose captif associée de ladite pluralité de molécules analogues de glucose captif ;

où quand une molécule de glucose dudit sujet passe à travers ladite au moins une région de surface formée d'une membrane semi-perméable et se fixe à ladite couche d'agglutination, une molécule luminescente déplacée et une molécule analogue de glucose captif associée se dirigent vers ladite région d'illumination dudit conteneur, et où l'illumination de toutes les molécules luminescentes déplacées et desdites molécules analogues de glucose captif associées à travers ladite région d'illumination produit une luminescence qui est associée au dit taux de glucose dudit fluide interstitiel.

29. Appareil de mesure du glucose *in vivo* par luminescence selon la revendication 28, dans lequel ledit taux de glucose dans ledit fluide interstitiel est sensiblement égal à un taux de glucose sanguin.

30. Appareil de mesure du glucose *in vivo* par luminescence selon la revendication 28, dans lequel ledit appareil est implanté dans une circulation sanguine dudit sujet.

31. Appareil de mesure du glucose *in vivo* par luminescence selon la revendication 28, dans lequel ladite pluralité de molécules luminescentes est inorganique.

32. Appareil de mesure du glucose *in vivo* par luminescence selon la revendication 28, dans lequel ledit conteneur est un tube de dialyse.

33. Appareil de mesure du glucose *in vivo* par luminescence selon la revendication 31, dans lequel une molécule luminescente de ladite pluralité de molécules luminescentes comprend en outre :

- ■ une boîte quantique ayant un coeur et une coque, ledit coeur étant choisi dans le groupe constitué par l'arséniure d'indium, le nitrure d'indium, le phosphure d'indium, le tellure de zinc, l'arséniure de gallium, l'antimoine de gallium,

l'antimoine d'indium et le sulfure de plomb, et ladite coque étant choisie dans le groupe constitué par le phosphure d'indium, le nitrure d'indium, le sulfure de cadmium, le séléniure de zinc, le sulfure de zinc, et le séléniure de plomb ;
■ au moins une molécule analogue de glucose captif ; et
■ au moins une molécule de liaison qui est hydrophile et qui est capable de se lier à ladite au moins une molécule analogue de glucose captif et à ladite boîte quantique.

34. Appareil de mesure du glucose *in vivo* par luminescence selon la revendication 33, dans lequel ladite au moins une molécule de liaison est choisie dans le groupe constitué par les acides mercapto-carboxyliques, les cyanures et les thiols.

35. Appareil de mesure du glucose *in vivo* par luminescence selon la revendication 33, dans lequel ladite molécule luminescente inorganique comprend en outre une coque externe hydrophile entourant ladite coque de ladite boîte quantique et à laquelle ladite au moins une molécule de liaison se lie.

36. Appareil de mesure du glucose *in vivo* par luminescence selon la revendication 35, dans lequel ladite coque externe hydrophile est organique.

37. Appareil de mesure du glucose *in vivo* par luminescence selon la revendication 36, dans lequel ladite coque externe hydrophile est choisie dans le groupe constitué par les acides mercaptocarboxyliques, les cyanures, les thiols, les tensioactifs et les bicouches lipidiques.

38. Appareil de mesure du glucose *in vivo* par luminescence selon la revendication 35, dans lequel ladite coque externe hydrophile est inorganique.

39. Appareil de mesure du glucose *in vivo* par luminescence selon la revendication 38, dans lequel ladite coque externe hydrophile est choisie dans le groupe constitué par le dioxyde de silicium, le nitrure de silicium, l'oxynitrure de silicium et l'oxyhydrure de silicium.

40. Appareil de mesure du glucose *in vivo* par luminescence selon la revendication 28, dans lequel ladite couche d'agglutination a une affinité pour le glucose et les analogues de sucre.

41. Appareil de mesure du glucose *in vivo* par luminescence selon la revendication 28, dans lequel ladite couche d'agglutination est la lectine.

42. Appareil de mesure du glucose *in vivo* par luminescence selon la revendication 28, dans lequel ladite couche d'agglutination est la concanavaline A.

43. Appareil de mesure du glucose *in vivo* par luminescence selon la revendication 28, dans lequel lesdites molécules analogues de glucose captif est un polysaccharide.

44. Appareil de mesure du glucose *in vivo* par luminescence selon la revendication 28, dans lequel ladite pluralité de molécules analogues de glucose captif est le dextrane.

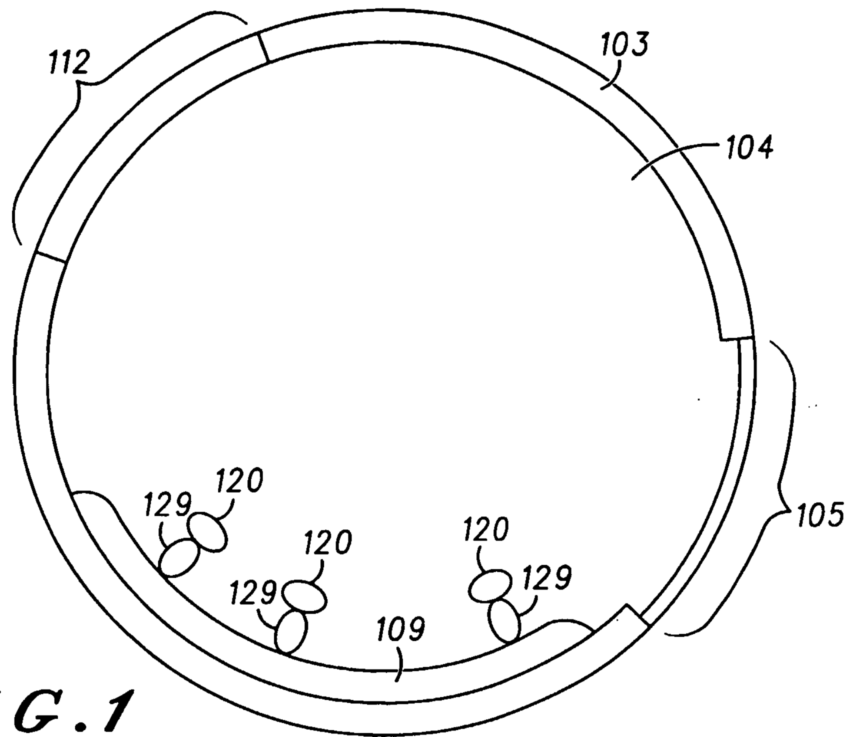

FIG.1

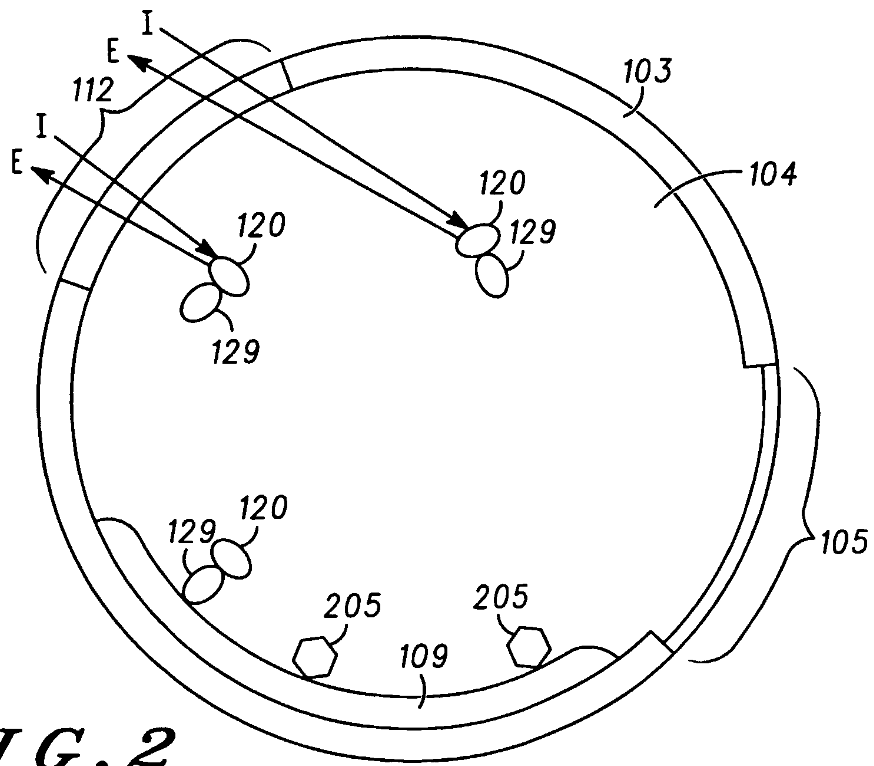

FIG.2

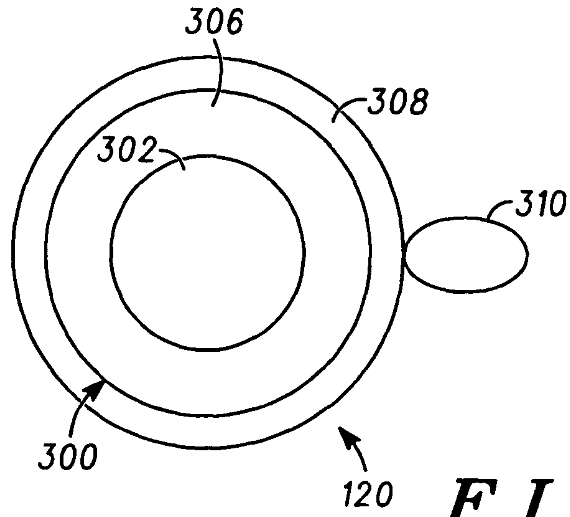

FIG.3A

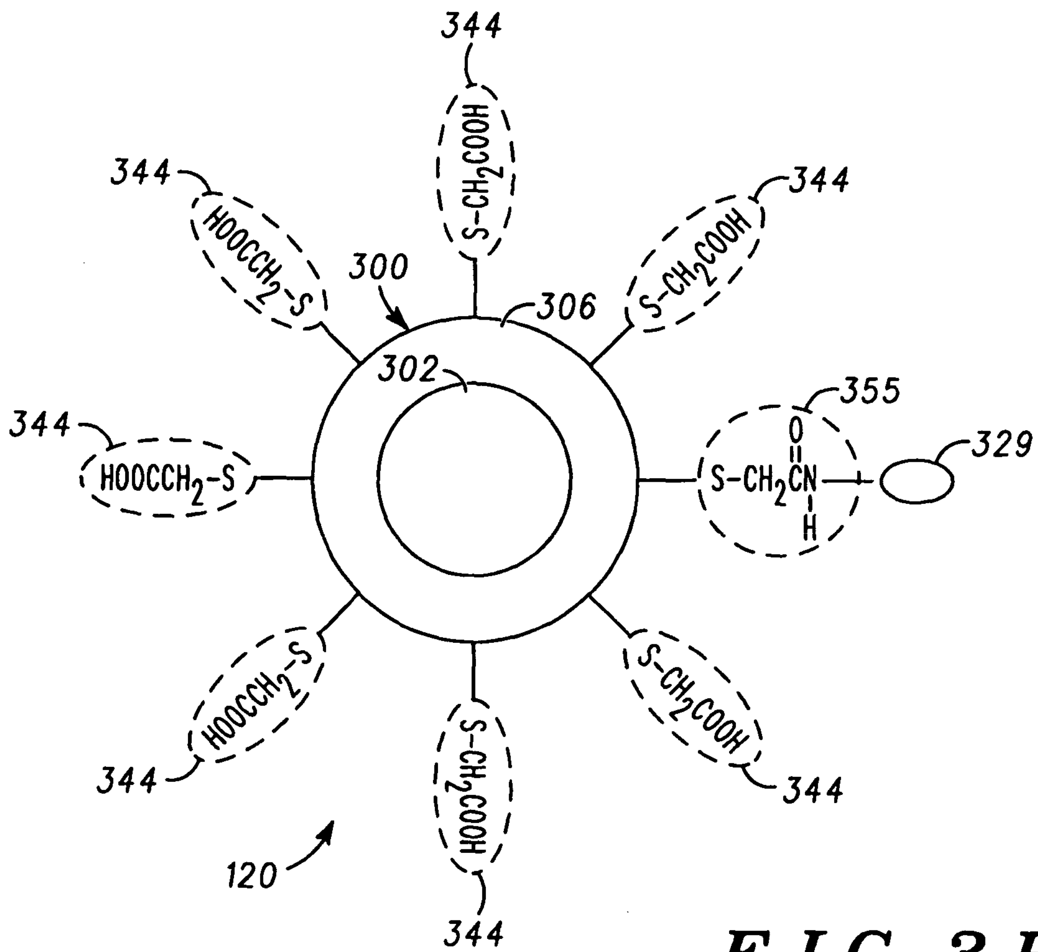

FIG.3B

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US 5001054 A **[0006]**

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专利名称(译)	发光体内葡萄糖测量		
公开(公告)号	EP1251780B1	公开(公告)日	2007-11-14
申请号	EP2001901819	申请日	2001-01-05
[标]申请(专利权)人(译)	摩托罗拉公司		
申请(专利权)人(译)	MOTOROLA , INC.		
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IPC分类号	A61B8/00 A61K9/22 A61K49/00 C12Q1/54 G01N33/53 A61B5/00 G01N33/66 A61B5/145 A61B5/1459 A61B10/00 G01N21/35		
CPC分类号	A61K49/0054 A61B5/14532 A61B5/1459 A61K49/0013 A61K49/0017 A61K49/0067 B82Y5/00 B82Y10/00 B82Y20/00		
代理机构(译)	MERCER , CHRISTOPHER PAUL		
优先权	09/489372 2000-01-21 US		
其他公开文献	EP1251780A1 EP1251780A4		
外部链接	Espacenet		

摘要(译)

提供了一种发光体内葡萄糖测量方法和装置（图1）。发光体内葡萄糖测量方法包括用照明光照射置换的发光分子（120），移位的发光分子和相关的捕获葡萄糖类似物分子（129）包含在植入的发光中的步骤<i>植入在受试者的组织间液内的体内测量装置，并测量发射的光，发射的光响应于照射而发射，其中发射的光与组织液中的葡萄糖水平相关。