**PCT** WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
**A61K 41/00, 31/74, 51/00, A61N 5/00, A23L 1/28**

**A1**

(11) International Publication Number: **WO 99/58149**

(43) International Publication Date: 18 November 1999 (18.11.99)

(21) International Application Number: PCT/US99/09584

(22) International Filing Date: 30 April 1999 (30.04.99)

(30) Priority Data:
09/078,329 13 May 1998 (13.05.98) US

(71) Applicant: LIGHT SCIENCES LIMITED PARTNERSHIP [US/US]; 1065 – 12th Avenue N.W. #E5, Issaquah, WA 98027 (US).

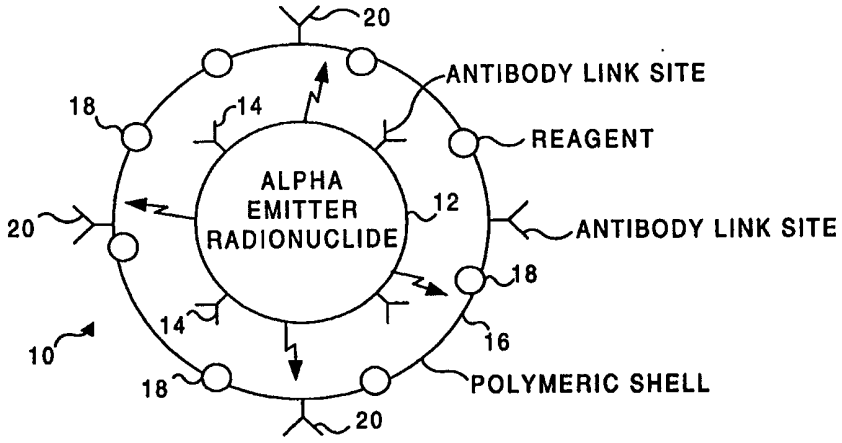
(72) Inventor: CHEN, James, C.; 2011 – 87th Place N.E., Bellevue, WA 98004 (US).

(74) Agent: ANDERSON, Ronald, M.; Law Offices of Ronald M. Anderson, Suite 507, 600 – 108th Avenue N.E., Bellevue, WA 98004 (US).

(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

**Published**
*With international search report.*
*Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

(54) Title: CONTROLLED ACTIVATION OF TARGETED RADIONUCLIDES




(57) Abstract

Abnormal tissue or malignant organelles within such tissue are destroyed by alpha particles emitted by radionuclide cores that are linked to the abnormal tissue. Targeted radionuclide beads each includes an alpha emitter radionuclide core (12) to which a plurality of antibody linking sites (14) are coupled. Surrounding the linking sites and radionuclide core is a polymeric shell (16) that absorbs alpha particles emitted by the core. A reagent (18) is applied to or included within the polymeric shell. Depending upon the material used for the reagent, it is activated by light of a particular waveband that is selectively applied after antibody linking sites (20) on the exterior of the shell have linked the targeted radionuclide to abnormal tissue in the body of a patient. Certain reagents are activated by light in a waveband corresponding to an absorption waveband of the reagent, while other types of reagents are activated by ultrasonic energy applied from an ultrasound source. When thus activated, the reagent causes fragmentation of the polymeric shell, enabling the alpha particles to pass into the abnormal tissue to which the radionuclide core becomes linked. The alpha particles destroy the abnormal tissue. It is also contemplated that the radionuclide core may instead emit beta particles, which though less toxic than alpha particles, can still destroy the targeted abnormal tissue.

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **AL** | Albania | **ES** | Spain | **LS** | Lesotho | **SI** | Slovenia |
| **AM** | Armenia | **FI** | Finland | **LT** | Lithuania | **SK** | Slovakia |
| **AT** | Austria | **FR** | France | **LU** | Luxembourg | **SN** | Senegal |
| **AU** | Australia | **GA** | Gabon | **LV** | Latvia | **SZ** | Swaziland |
| **AZ** | Azerbaijan | **GB** | United Kingdom | **MC** | Monaco | **TD** | Chad |
| **BA** | Bosnia and Herzegovina | **GE** | Georgia | **MD** | Republic of Moldova | **TG** | Togo |
| **BB** | Barbados | **GH** | Ghana | **MG** | Madagascar | **TJ** | Tajikistan |
| **BE** | Belgium | **GN** | Guinea | **MK** | The former Yugoslav Republic of Macedonia | **TM** | Turkmenistan |
| **BF** | Burkina Faso | **GR** | Greece | | | **TR** | Turkey |
| **BG** | Bulgaria | **HU** | Hungary | **ML** | Mali | **TT** | Trinidad and Tobago |
| **BJ** | Benin | **IE** | Ireland | **MN** | Mongolia | **UA** | Ukraine |
| **BR** | Brazil | **IL** | Israel | **MR** | Mauritania | **UG** | Uganda |
| **BY** | Belarus | **IS** | Iceland | **MW** | Malawi | **US** | United States of America |
| **CA** | Canada | **IT** | Italy | **MX** | Mexico | **UZ** | Uzbekistan |
| **CF** | Central African Republic | **JP** | Japan | **NE** | Niger | **VN** | Viet Nam |
| **CG** | Congo | **KE** | Kenya | **NL** | Netherlands | **YU** | Yugoslavia |
| **CH** | Switzerland | **KG** | Kyrgyzstan | **NO** | Norway | **ZW** | Zimbabwe |
| **CI** | Côte d'Ivoire | **KP** | Democratic People's Republic of Korea | **NZ** | New Zealand | | |
| **CM** | Cameroon | | | **PL** | Poland | | |
| **CN** | China | **KR** | Republic of Korea | **PT** | Portugal | | |
| **CU** | Cuba | **KZ** | Kazakstan | **RO** | Romania | | |
| **CZ** | Czech Republic | **LC** | Saint Lucia | **RU** | Russian Federation | | |
| **DE** | Germany | **LI** | Liechtenstein | **SD** | Sudan | | |
| **DK** | Denmark | **LK** | Sri Lanka | **SE** | Sweden | | |
| **EE** | Estonia | **LR** | Liberia | **SG** | Singapore | | |

# CONTROLLED ACTIVATION OF TARGETED RADIONUCLIDES

## Field of the Invention

The present invention generally relates to the use of a radioactive substance to destroy abnormal tissue within a patient's body, and more specifically, to the use of radionuclides that are bound with antibodies specifically targeted to link with the abnormal tissue.

## Background of the Invention

One of the arsenal of weapons currently available to combat cancer employs radiation emitting materials (radionuclides) that are injected into a patient's body to identify and/or to destroy abnormal or malignant tissue. Antibodies are typically bound to the radionuclides to target the abnormal tissue, by linking the radiation emitting material to the surface of malignant cell organelles. To identify and diagnose the presence of a tumor with radionuclides that link to tumor cells and emit $\gamma$ rays, immunoscintigraphy is employed to produce an image of a suspected site with a $\gamma$ camera or scintigraphic scanner. An intensity distribution of the site is converted into a corresponding image on a photographic film plate or displayed on a computer monitor screen and may be visually enhanced by appropriate computer processing. Details of this procedure are reported by M. Magerstadt in Chapter 2 of his book Antibody Conjugates and Malignant Disease, which is entitled "Immunoconjugates for *In Vivo* Tumor Diagnosis," CRC Press, Inc., 1991.

A somewhat different approach is used when radionuclides are intended to destroy tumor cells. In the past, targeted sources that emit beta particles rather than alpha particles have been preferred for this purpose, since such sources are more readily available and are relatively easy to safely handle. The toxicity of alpha particles is much greater than that of beta particles; in fact, even a single alpha particle can destroy a cell. Alpha particles are readily blocked by even a single sheet of paper, and in the body, will travel only through the membrane of a single adjacent cell or cell organelle before being absorbed. By injecting a targeted alpha source radionuclide material into or immediately adjacent to a

tumor site, the damage to normal tissue surrounding the tumor is greatly minimized.

However, unbound targeted radionuclides that escape linkage to tumor cells tend to be carried throughout a patient's body, passing through organ systems in which they can cause substantial damage. Bone marrow, lung tissue, liver tissue, and the renal system are particularly susceptible to damage from such unbound radionuclides. Because of concerns about damage to these organ systems, the dosage of targeted radionuclides administered to a patient is normally relatively limited, particularly when the radionuclide emits alpha particles. The requirement for such limitation is unfortunate, because the lethal effect of alpha particles in destroying abnormal tissue is well established. Clearly, it would be preferable to develop a technique for administering targeted radionuclides in larger dosages without increasing the likelihood of damage to normal cells.

## Summary of the Invention

In accord with the present invention, a method for destroying abnormal tissue within a patient's body is defined. The method includes the step of providing a radionuclide that emits radiation having a lethal effect on the abnormal tissue. Before it is administered to the patient, the radionuclide is enclosed within a shell of a material that blocks the radiation emitted by the radionuclide. However, the shell includes a reagent adapted to be selectively activated and when thus activated, causes the shell to be breached, enabling the radiation emitted by the radionuclide to pass without blockage by the shell. A binding agent is applied to the shell, producing a targeted radionuclide. The binding agent is selected so that the shell preferentially links to the abnormal tissue, but not to normal tissue. The targeted radionuclide is then administered to a patient, preferably either at a treatment site where the abnormal tissue is believed to be disposed, or proximate thereto. The binding agent links the radionuclide to the abnormal tissue. Once the preceding steps are completed, the reagent is selectively activated, causing the shell to be breached. Breaching of the shell enables the radiation emitted by the radionuclide to destroy the abnormal tissue.

The radiation emitted by the radionuclide preferably comprises alpha particles, since they are readily blocked by the material of the shell; however, a radionuclide that emits beta particles is also usable in the present invention.

Alternative approaches are contemplated for breaching the shell to enable the radiation to reach the abnormal tissue. In one embodiment, the reagent comprises an ultrasonic reactive material that is activated when exposed to

ultrasonic energy. In this case, the step of activating comprises the steps of providing an ultrasonic energy source, and directing the ultrasonic energy emitted by the source at the targeted radionuclide material after the binding agent has linked the targeted radionuclide material to the abnormal tissue.

In an alternative embodiment, the reagent includes a photoreactive material that is activated when exposed to light. In this case, the step of activating includes the steps of providing a light source, and illuminating the targeted radionuclide material with light emitted by the light source, after the binding agent has linked the targeted radionuclide material to the abnormal tissue. In one preferred form of this embodiment, the light source emits light that is within a predefined waveband selected because the photoreactive material is activated by light within that waveband. To administer the light to the targeted radionuclide, the light source can be implanted within the patient's body, adjacent to the abnormal tissue, or may be disposed externally to the patient's body, so that the light emitted by the source penetrates through tissue to the abnormal tissue and the targeted radionuclide that is bound to the abnormal tissue.

The shell comprises a polymer in one form of the invention. More specifically, the shell may comprise lignan. In addition, the reagent may comprise either Methylene Blue photoreactive material or Bengal Rose photoreactive material.

The method may also include the step of applying the binding agent to the radionuclide before the radionuclide is enclosed within the shell. In this embodiment, the binding agent applied to the radionuclide preferentially links the radionuclide to the abnormal tissue when the shell is breached by activating the reagent. This approach minimizes the risk that the radionuclide will be carried away from the abnormal tissue, to other parts of the patient's body.

It is preferable that, so long as the reagent is not activated, the material of the shell be selected to ensure that the shell remains intact until after the targeted radionuclide is naturally eliminated from the patient's body. Furthermore, the radionuclide should be selected to have a relatively short half life to ensure that if the reagent is not activated, the radionuclide ceases to emit radiation before the shell degrades sufficiently so that it no longer encloses the radionuclide.

A further aspect of the present invention is directed to a therapeutic construct for use in destroying abnormal tissue within a patient's body. The therapeutic construct comprises components that are generally consistent in functionality with steps of the method discussed above.

## Brief Description of the Drawing Figures

The foregoing aspects and many of the attendant advantages of this invention will become more readily appreciated as the same becomes better understood by reference to the following detailed description, when taken in conjunction with the accompanying drawings, wherein:

FIGURE 1 schematically illustrates a first embodiment of a targeted radionuclide in accord with the present invention;

FIGURE 2A is schematic view of the targeted radionuclide bound to a target malignant cell organelle;

FIGURE 2B is a schematic view of the targeted radionuclide of FIGURE 2A, showing a reagent being activated by either light or ultrasound energy;

FIGURE 2C is a schematic view showing the activated reagent fragmenting a shell around a radionuclide core;

FIGURE 2D is a schematic diagram illustrating the radionuclide core of FIGURE 2C bound to the target malignant cell or organelle and emitting alpha particles to destroy the malignant tissue;

FIGURE 3 is a schematic cross-sectional view of a portion of a patient's body in which a tumor is disposed, showing beads of targeted radionuclide being injected into and around the tumor with a syringe;

FIGURE 4 is a schematic view showing a second embodiment of the targeted radionuclide bead;

FIGURE 5 is a schematic view showing a third embodiment of the targeted radionuclide bead;

FIGURE 6 is a schematic cross-sectional view of a portion of a blood vessel into which targeted radionuclide beads are being injected;

FIGURE 7 is a schematic cross-sectional view of a portion of a patient's body containing a tumor, showing an external infrared light source being used to activate the reagent in targeted radionuclide beads that are linked to the abnormal tissue in the tumor;

FIGURE 8 is a schematic cross-sectional view of a portion of a patient's body containing a tumor, showing an internal light source being used to activate the reagent in targeted radionuclide beads that are linked to the abnormal tissue in the tumor;

FIGURE 9 is a schematic cross-sectional view of a portion of a patient's body containing a tumor, showing an external ultrasonic wave source being used

to activate the reagent in targeted radionuclide beads that are linked to the abnormal tissue in the tumor; and

FIGURE 10 is a schematic cross-sectional view of a portion of a patient's body containing a tumor, showing an internal ultrasonic wave source being used to activate the reagent in targeted radionuclide beads that are linked to the abnormal tissue in the tumor.

## Description of the Preferred Embodiments

Overview of the Invention

Referring to FIGURE 1, a targeted radionuclide bead 10 in accordance with the present invention is schematically illustrated. The targeted radionuclide includes an alpha emitter radionuclide core 12 that includes a suitable alpha emitting material. Table 1 identifies isotopes of Bi, At, and Rn that are suitable for use in the radionuclide core, based upon their relatively short half life. However, it is also contemplated that other types of alpha emitting materials can be used for the radionuclide core. In addition, since the present invention can also be used in connection with a radionuclide core material that emits beta particles, Table 1 includes the half life of several such materials.

Attached to the surface of radionuclide core 12 are a plurality of antibody linking sites 14, which are specifically targeted to link with antigens on abnormal tissue or malignant cell organelles within a patient's body. Antibody linking sites 14 and radionuclide core 12 are enclosed within a polymeric shell 16 formed of a polymer that is biocompatible and sufficiently thick to absorb alpha particles emitted by radionuclide core 12 so that the alpha particles do not travel beyond the polymeric shell. Thus, outside polymeric shell 16, it is generally not possible to detect any significant alpha particle radiation emitted by the radionuclide core.

**TABLE 1**

| Radionuclide Core Isotopes | Type Of Particle Emitted | Half-Life |
|---|---|---|
| 212 Bi | α | 1 hr. |
| 212 At | α | 7 hr. |
| 222 Rn | α | 3.8 days |
| Tritium | β | 12 yr. |
| 198 Au | β | 2.7 days |
| 32 P | β | 14 days |
| 90 Y | β | 2.6 days |
| 90 Sr | β | 28 years |

Incorporated into or applied to polymeric shell 16 is a reagent 18 that is selected for its characteristic reaction when exposed to either light or ultrasound energy. In one embodiment, when exposed to light within a waveband corresponding to its characteristic absorption waveband, reagent 18 absorbs the energy of the light, becomes activated, and causes polymeric shell 16 to fragment. Alternatively, in another embodiment, reagent 18 is characterized by its response to ultrasound energy; when activated by exposure to the ultrasound energy, the reagent fragments polymeric shell 16. Clearly, different types of reagents having different absorption wavebands can be used to respond to light of different wavebands or to respond to ultrasound energy. The proportion of a particular reagent used relative to the polymeric material of the shell will determine how rapidly the shell is fragmented when the reagent is activated. The surface of polymeric shell 16 includes a plurality of antibody linking sites 20, which are also targeted to bind to abnormal tissues or malignant cell organelles within a patient's body.

FIGURES 2A-2D illustrate how targeted radionuclide bead 10 is used for destroying a malignant cell organelle 22. In FIGURE 2A, the targeted radionuclide is shown with one of the antibody link sites 20 linked to an antigen 24 that is associated with the malignant cell organelle. Because normal cells do not have any antigen to which antibody link sites 20 will couple, targeted radionuclide beads 10 do not become bound to normal cells. After providing sufficient time for the targeted radionuclide beads to bind to the malignant cell organelles or abnormal tissue within a patient's body, light in an appropriate waveband or ultrasound energy 26 is applied generally as illustrated in FIGURE 2B, using one of the techniques disclosed hereinbelow. The light or ultrasound energy activates reagent 18. As shown in FIGURE 2C, an activated reagent 18' causes shell 16 to fragment, creating shell fragments 16' (that are flushed away from radionuclide core 12 by bodily fluids). Finally, as illustrated in FIGURE 2D, antibody link sites 14 on radionuclide core 12 become bound to antigens 24 on the malignant cell organelle immediately adjacent to the radionuclide core. Alpha particles emitted by radionuclide core 12 are no longer absorbed by polymeric shell 16, but instead, penetrate the malignant cell organelle or abnormal tissue, destroying it.

Injection of Targeted Radionuclide Beads

Targeted radionuclide beads 64 are most expediently infused into or adjacent to a tumor or other abnormal tissue at a treatment site when suspended in a biocompatible fluid, such as a physiological saline solution. As shown in a

partial cross section view 50 in FIGURE 3, a syringe 58 can be used for injecting such a fluid containing targeted radionuclide beads 64 into a tumor 66, which is disposed inside a patient's body. A needle 60 that is connected to syringe 58 is inserted through an epidermal layer 52 and a dermal layer 54 into tumor 66. Dash lines 62 illustrate previous injection sites where targeted radionuclide beads 64 have been injected directly into and in the vicinity of tumor 66. Once targeted radionuclide beads 64 are thus infused at spaced-apart locations adjacent to (or within) tumor 66, a light source that emits IR light is activated, causing the reagent to be activated so that the shell surrounding the radionuclide core of the beads is fragmented. The radionuclide core then becomes linked to the abnormal tissue or cells comprising the tumor. Furthermore, the fragmentation of the shell around each radionuclide core enables the alpha particles emitted by the radionuclide material in the core to enter the adjacent abnormal cell or organelle, destroying it.

As an abnormal cell is destroyed, the antibody link sites on the radionuclide core becomes linked to an antigen on another abnormal cell or cell organelle. That abnormal cell is then destroyed by the alpha particles emitted by the radionuclide core. This process repeats until the tumor is substantially eliminated or at least greatly reduced in size.

Referring to FIGURE 4, a targeted radionuclide bead 10' is illustrated that includes radionuclide core 12, antibody linking sites 14 coupled to the outer surface of the radionuclide core, and a shell that includes an inner Methylene Blue shell or coat in which Methylene Blue 32 is dispersed, and an outer lignan shell 36. One source of lignan is wood fibers that have been exposed to alkaline hydrogen peroxide bleach in a thermomechanical reactor process.

Several studies have determined that lignan breaks down when attacked by singlet oxygen sensitized by compounds such as Methylene Blue and Bengal Rose. The singlet oxygen appears to have a role in the photodegradation of lignan or in a photo-oxidation of phenols in the lignan that cause its degradation. A more complete explanation of this process is disclosed in "Photodegradation of Lignan: The Role of Singlet Oxygen." by C. Crestini and M. D'Auria, Journal of Photochemistry and Photobiology A: Chemistry 101 (1996), pp. 69-73. Also see "Photochemically Induced Solid-State Degradation, Condensation, and Rearrangement Reactions in Lignan Model Compounds and Milled Wood Lignan," D. Argyropoulos and Y. Sun, Photochemistry and Photobiology (1996) 64(3) pp. 510-517. The Methylene Blue shell or coat preferably includes molecules of O2 as the source of the singlet oxygen produced

when the Methylene Blue is exposed to light of an appropriate wavelength. Bengal Rose and other photodynamic agents can be used instead of Methylene Blue in much the same way to support the fragmentation of lignan shell 36 in response to activation by light of the required waveband corresponding to an absorption waveband of the Methylene Blue or other photoreactive agent. In FIGURE 5, yet a different configuration is illustrated in which the Methylene Blue 40 and lignan are combined in an outer shell 38 surrounding an inner shell 42, comprising a fluid that is trapped within the compound shell when the radionuclide core was encapsulated in the compound shell. Targeted radionuclide beads 10" are also activated by light of the appropriate waveband corresponding to an absorption waveband of the Methylene Blue or other photoreactive agent that produces singlet oxygen to fragment the lignan shell. It should be noted that photoreactive agents (or other types of reagents) using a different process that does not produce singlet oxygen may be used for fragmenting a polymeric shell surrounding radionuclide core 12 in response to light energy of an appropriate waveband that is absorbed by the reagent to activate it.

While it is generally preferable to parentally introduce the targeted radionuclide beads as close as possible to a treatment site where abnormal tissue is to be destroyed, as illustrated in FIGURE 6, it is also contemplated that syringe 58 can be used to inject a fluid containing the targeted radionuclide beads in suspension through a dermal layer 70 and into a bloodstream 72. Needle 60 passes through dermal layer 70 and through a wall 76 of bloodstream 72, conveying the fluid containing the targeted radionuclide beads into blood 74; the flowing blood carries the targeted radionuclide beads downstream to an organ in which the abnormal tissue is disposed. It is also contemplated that in cases where metastases of has occurred, causing malignant cells to disperse throughout a patient's body, hypodermic injection of the targeted radionuclide beads into the patient's vascular system can be used to more pervasively distribute them throughout the patient's body so that they become linked to the dispersed abnormal cells or malignant organelles. It is important to note that by carefully selecting the material used for polymeric shell 16 so that it does not degrade prior to the time that the targeted radionuclide beads are excreted from the patient's body, and by carefully selecting the material used for radionuclide core 12 to have a sufficiently short half life, injury to normal tissue can be minimized. Such injury will only occur in those cases where the targeted radionuclide beads permit the alpha particles emitted by the core to reach normal tissue.

Activation of Reagent

An important step in enabling the alpha particles to destroy abnormal tissue is the activation of the reagent so that the shell surrounding the radionuclide core is fragmented or degraded after the targeted radionuclide has linked to the abnormal tissue. It should be noted that shell thickness can be varied to account for degradation due to the radionuclide alone. In addition, the proportion of the polymeric shell material to the reagent can be varied to achieve a desired degree of stability. In any case, activation of the reagent to fragment the shell must occur before the radionuclide core becomes too "cool" to destroy abnormal tissue to which the radionuclide core is bound.

In FIGURE 7, a tumor 140 has been infused with targeted radionuclide beads 64. The beads can be infused either within a biocompatible fluid, such as a physiological saline solution, or can be applied topically to the exterior surface of tumor 140. Tumor 140 lies within the patient's body, adjacent a dermal layer 144. Outside the patient's body, a power supply 150 is coupled through a lead 148 to an external IR LED array 146. Array 146 comprises a plurality of IR LEDs 152 arranged in spaced-apart array. When energized by power supply 150, LEDs 152 emit IR light 154 that passes freely through the dermal layer and into tumor 140, activating the reagent that is included within beads 64 so that the shell surrounding the alpha particle emitting radionuclide core is fragmented. After the shell is fragmented, the radionuclide core becomes bound to the abnormal cells, and the alpha particles emitted by the radionuclide material destroys tumor 140.

FIGURE 8 illustrates yet another technique for exposing beads 64 to IR light. In this approach, a probe 160 is disposed interstitially within tumor 140. Probe 160 includes a linear array 162 of the IR LEDs that are energized through a lead 164; lead 164 is coupled to a remote internal (or external) power supply (not shown). If disposed internally, the power supply mentioned in regard to FIGURES 7 and 8 can be energized using an external power source that is electromagnetically coupled to the internal power supply. A detailed description of apparatus suitable for providing such electromagnetic coupling is described in U.S. Patent No. 5,715,837, which is assigned to the same assignee as the present invention.

As noted above, materials are also available for use as a reagent to fragment the polymeric shell surrounding radionuclide core 12 in response to absorption of ultrasonic energy. Examples of reagents that are activatable by ultrasound energy include hematoporphyrin, gallium-deuteroporphyrin complex, and cobalamins. In FIGURE 9, tumor 140 to which targeted radionuclide beads

are linked is shown at a site within a patient's body. An ultrasonic driver 100 is coupled through a cable 102 to an ultrasonic wave source 104. Ultrasonic transducers for use in producing ultrasonic waves 106 are well known in the medical art and are often used in connection with sensors for receiving reflected ultrasonic waves to image internal structure within a patient's body. However, for use with the present invention, the ultrasonic wave source or transducer is only needed to transmit ultrasonic waves that act upon the reagent comprising each of the targeted radionuclide beads, causing the polymeric shell surrounding the radionuclide cores of the beads to fragment. Once the polymeric shell is fragmented (as generally illustrated in FIGURES 2C-2D), the alpha particles emitted by the radionuclide core destroy the abnormal tissue or malignant organelles to which they have become linked. As shown in FIGURE 9, ultrasonic waves 106 readily penetrate dermal layer 144 and are thus able to reach and activate targeted radionuclide beads 64 on tumor 140 within the body of a patient.

FIGURE 10 illustrates targeted radionuclide beads 64 linked to tumor 140. The reagent in each bead fragments the shell of the bead when activated using ultrasonic waves 106 that are emitted by a plurality of spaced-apart ultrasonic transducer chips 112 disposed on an internal, interstitial ultrasonic probe 110. Energy is supplied to the probe from an internal or external ultrasonic driver (not separately shown) through a lead 114 so that it produces ultrasonic waves 106. The internal, interstitial ultrasonic probe is hermetically sealed and is introduced surgically (or endoscopically) into the proximity of tumor 140 so that the ultrasonic energy emitted by the probe activates the reagent in each of the targeted radionuclide beads, enabling alpha particles to be emitted from the radionuclide core of the beads, to destroy the tumor cells.

Although the present invention has been described in connection with the preferred form of practicing it, those of ordinary skill in the art will understand that many modifications can be made thereto within the scope of the claims that follow. Accordingly, it is not intended that the scope of the invention in any way be limited by the above description, but instead be determined entirely by reference to the claims that follow.

The invention in which an exclusive right is claimed is defined by the following:

1. A method for destroying abnormal tissue within a patient's body, comprising the steps of:

(a) providing a radionuclide that emits radiation having a lethal effect on the abnormal tissue;

(b) enclosing the radionuclide within a shell of a material that blocks the radiation emitted by the radionuclide, said material including a reagent adapted to be selectively activated and when thus activated, to cause the shell to be breached, enabling the radiation emitted by the radionuclide to pass without blockage by the shell;

(c) applying a binding agent to the shell, producing a targeted radionuclide, said binding agent being selected so that the shell preferentially links to the abnormal tissue, but not to normal tissue;

(d) administering the targeted radionuclide to a patient, said binding agent selectively linking the radionuclide to the abnormal tissue; and

(e) activating the reagent, causing the shell to be breached, thereby enabling said radionuclide to emit the radiation, to destroy the abnormal tissue.

2. The method of Claim 1, wherein the radionuclide comprises a material that emits either alpha particles or beta particles.

3. The method of Claim 1, wherein the reagent comprises an ultrasonic reactive material that is activated when exposed to ultrasonic energy.

4. The method of Claim 3, wherein the step of activating comprises the steps of providing an ultrasonic energy source; and, directing the ultrasonic energy emitted by the ultrasonic energy source at the targeted radionuclide material after said binding agent has linked the targeted radionuclide material to the abnormal tissue.

5. The method of Claim 1, wherein the reagent comprises a photoreactive material that is activated when exposed to light.

6. The method of Claim 5, wherein the step of activating comprises the steps of providing a light source; and, illuminating the targeted radionuclide material with light emitted by the light source after said binding agent has linked the targeted radionuclide material to the abnormal tissue.

7. The method of Claim 6, wherein the light source emits light that is within a predefined waveband, said photoreactive material being activated by the light within said predefined waveband.

8. The method of Claim 6, wherein the step of providing the light source comprises the step of implanting the light source within the patient's body, adjacent to the abnormal tissue.

9. The method of Claim 1, wherein the shell comprises a polymer.

10. The method of Claim 1, wherein the shell comprises lignan.

11. The method of Claim 1, wherein the reagent comprises one of a Methylene Blue photoreactive material and a Bengal Rose photoreactive material.

12. The method of Claim 1, further comprising the step of also applying the binding agent to the radionuclide before the radionuclide is enclosed within the shell, said binding agent applied to the radionuclide preferentially linking the radionuclide to the abnormal tissue when the shell is breached by activating the reagent.

13. The method of Claim 1, wherein the material of the shell is selected to ensure that the shell remains intact until after the targeted radionuclide is naturally eliminated from the patient's body, so long as the reagent is not activated.

14. The method of Claim 1, wherein the radionuclide is selected to have a relatively short half life to ensure that if the reagent is not activated, the radionuclide ceases to emit radiation before the shell degrades sufficiently so that it no longer encloses the radionuclide.

15. A therapeutic construct for use in destroying abnormal tissue within a patient's body, comprising:

(a) a radionuclide substance that emits radiation having a lethal effect on the abnormal tissue;

(b) a shell of a material that blocks the radiation emitted by the radionuclide, said shell enclosing the radionuclide;

(c) a reagent included within the shell, said reagent causing the shell to be fragmented when the reagent is selectively activated, enabling the radiation emitted by the radionuclide to pass without being blocked by the shell; and

(d) a binding agent disposed on a surface of the shell, said binding agent being selected to preferentially link to the abnormal tissue, but not to normal tissue, said shell, said radionuclide, and said binding agent together comprising a targeted radionuclide that is adapted to be administered to a patient, bind to the abnormal tissue in the patient's body, and when the reagent is activated, expose the abnormal tissue to the radiation emitted by the radionuclide, destroying the abnormal tissue.

16. The therapeutic construct of Claim 15, wherein the radiation emitted by the radionuclide comprises either alpha particles or beta particles.

17. The therapeutic construct of Claim 15, wherein the reagent comprises an ultrasonic reactive material that is activated when exposed to ultrasonic energy.

18. The therapeutic construct of Claim 15, wherein the reagent comprises a photoreactive material that is activated when exposed to light.

19. The therapeutic construct of Claim 15, wherein the shell comprises a polymer.

20. The therapeutic construct of Claim 15, wherein the shell comprises lignan.

21. The therapeutic construct of Claim 15, wherein the reagent comprises one of a Methylene Blue photoreactive material, and a Bengal Rose photoreactive material.

22. The therapeutic construct of Claim 15, further comprising another binding agent disposed on the radionuclide, said other binding agent being selected to preferentially link the radionuclide to the abnormal tissue after the shell has been fragmented by activating the reagent.

23. The therapeutic construct of Claim 15, wherein the material of the shell is selected to ensure that the shell remains intact until after the targeted radionuclide is naturally eliminated from the patient's body, so long as the reagent is not activated.

24. The therapeutic construct of Claim 15, wherein the radionuclide is selected to have a relatively short half life to ensure that if the reagent is not activated, the radionuclide ceases to emit radiation before the shell degrades sufficiently so that it no longer encloses the radionuclide.

25. The therapeutic construct of Claim 15, wherein the reagent breaks down the material of the shell when the reagent is activated, exposing the radionuclide so that the radiation emitted thereby penetrates the abnormal tissue adjacent to the radionuclide.

26. A method for delivering a radionuclide to a treatment site to destroy abnormal tissue within a patient's body, without harming normal tissue, comprising the steps of:

(a) enclosing the radionuclide within a shell that blocks the radiation, preventing the radiation from penetrating the normal tissue, said shell including a reagent that is selectively activatable, such that when activated, the reagent breaches the shell, enabling the radiation emitted by the radionuclide to pass without being blocked by the shell;

(b) administering the radionuclide to the patient while it is enclosed by the shell, so that it reaches the treatment site without harming normal tissue; and

(c) activating the reagent after the radionuclide has reached the treatment site, enabling the radiation emitted by the radionuclide to penetrate the abnormal tissue.

27. The method of Claim 26, further comprising the step of applying a binding agent to the shell that specifically preferentially targets and links to the abnormal tissue, but not to normal tissue, said binding agent causing the shell to be linked to the abnormal tissue at the treatment site.

28. The method of Claim 27, wherein the binding agent comprises an antibody.

29. The method of Claim 26, further comprising the step of applying a binding agent to the radionuclide before the radionuclide is enclosed within the shell, said binding agent preferentially targeting and linking to the abnormal tissue at the treatment site, rather than to normal tissue.

30. The method of Claim 29, wherein the binding agent comprises an antibody.

31. The method of Claim 26, wherein the reagent is activated by one of an ultrasonic signal and a light signal.

32. The method of Claim 26, wherein the reagent comprises one of a Methylene Blue and a Bengal Rose photoreactive agent.

33. The method of Claim 26, wherein the shell comprises a polymer.

34. The method of Claim 33, wherein the shell comprises lignan.

35. The method of Claim 26, wherein the radionuclide enclosed within the shell is administered to the patient within a vascular passage and conveyed to the treatment site within a vascular fluid.

36. The method of Claim 26, wherein radionuclides enclosed within a shell in which the reagent is not activated and not retained at the treatment site are naturally excreted from the patient's body.

37. The method of Claim 26, wherein the radiation emitted by the radionuclide comprises alpha particles and the radionuclide has a half life that is substantially less than a time required for the shell to degrade within the patient's body.

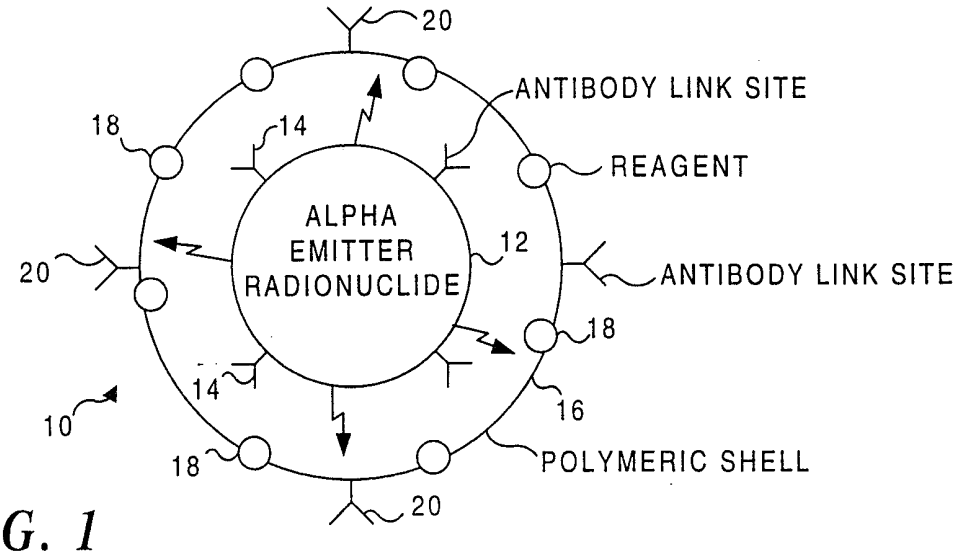



FIG. 1

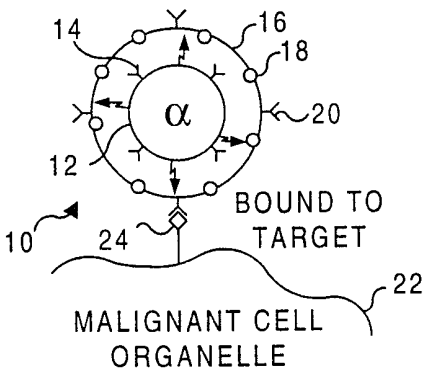



FIG. 2A

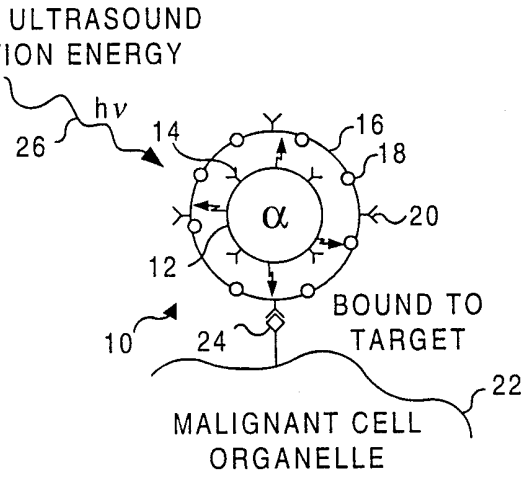



FIG. 2B

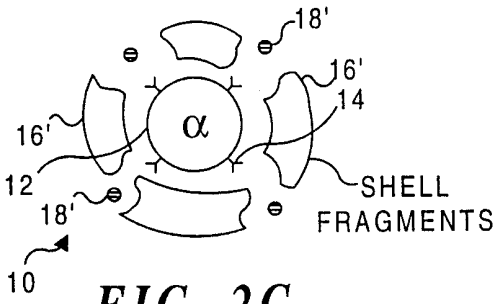



FIG. 2C

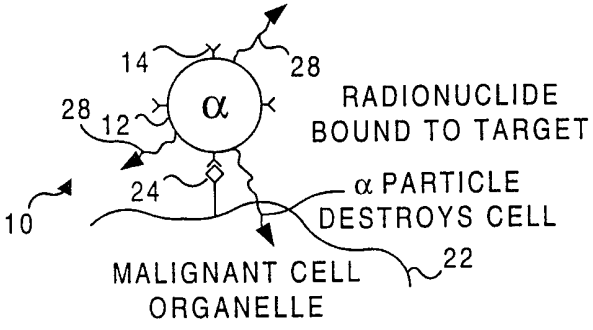



FIG. 2D

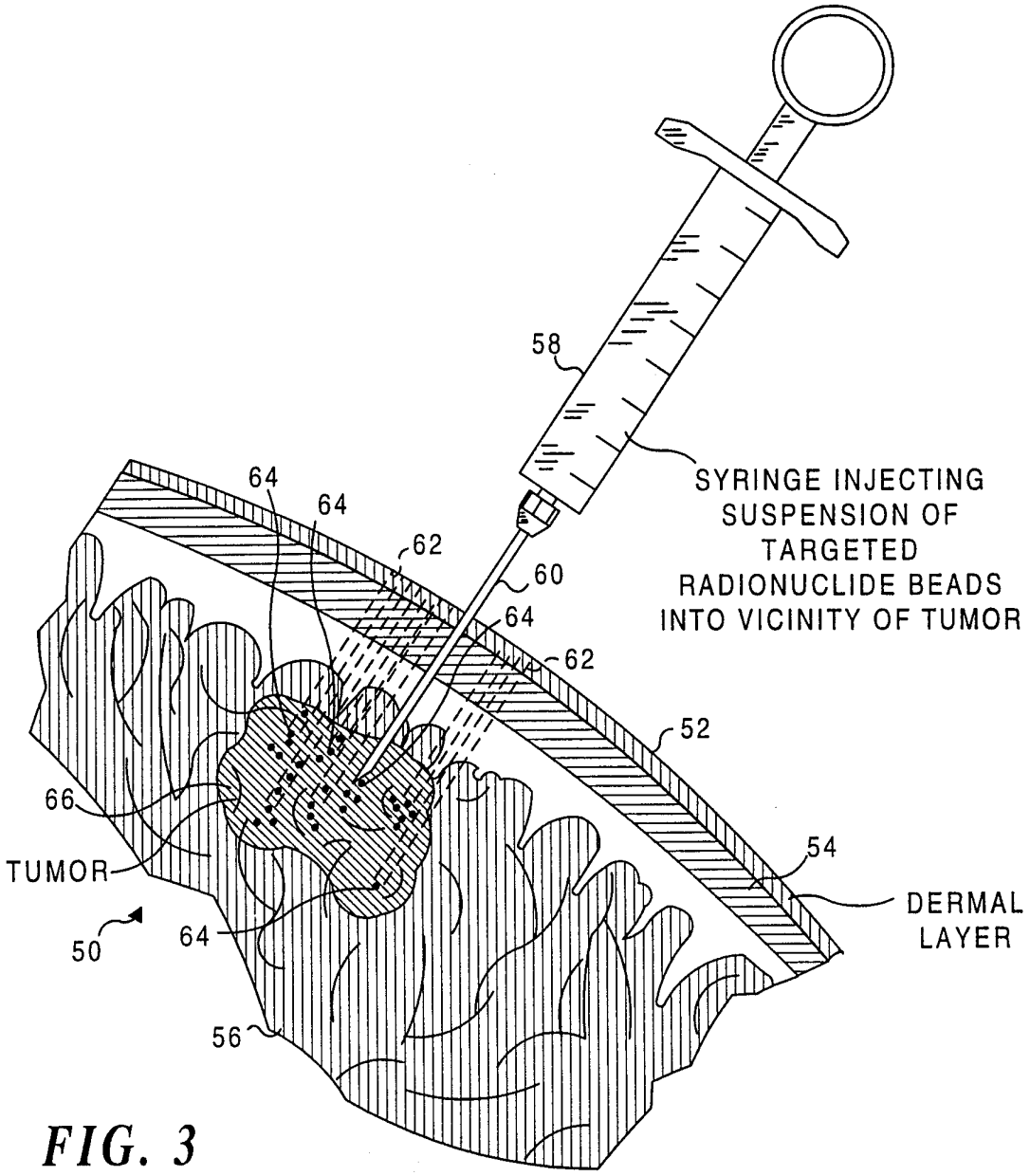

58
SYRINGE INJECTING SUSPENSION OF TARGETED RADIONUCLIDE BEADS INTO VICINITY OF TUMOR
64
64
62
60
64
62
52
66
TUMOR
54
DERMAL LAYER
50
64
56

*FIG. 3*

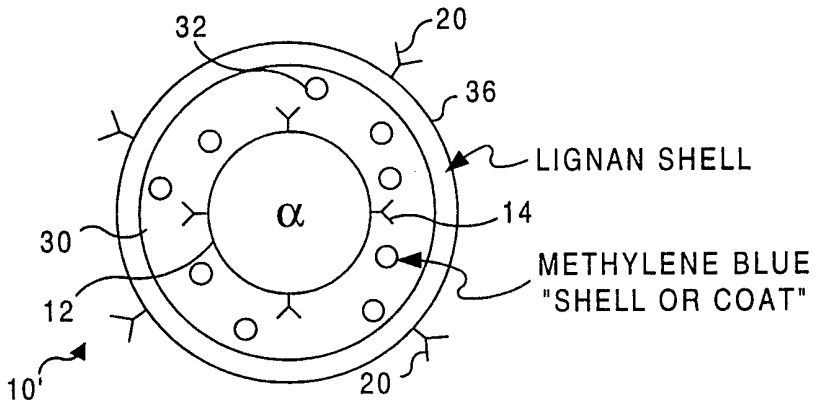

32
20
36
LIGNAN SHELL
α
14
30
METHYLENE BLUE "SHELL OR COAT"
12
10'
20

*FIG. 4*

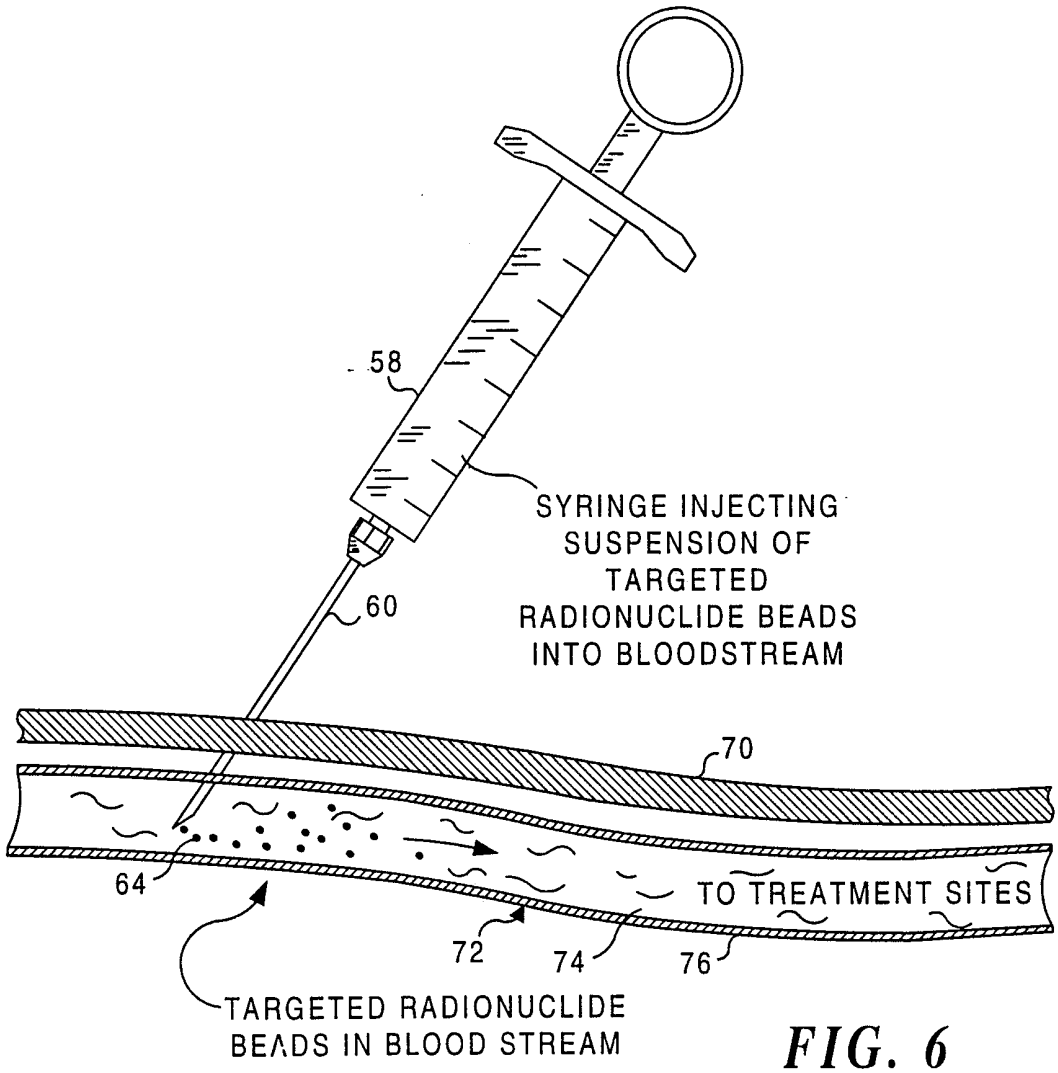

58
SYRINGE INJECTING SUSPENSION OF TARGETED RADIONUCLIDE BEADS INTO BLOODSTREAM
60
70
64
TO TREATMENT SITES
72
74
76
TARGETED RADIONUCLIDE BEADS IN BLOOD STREAM

*FIG. 6*

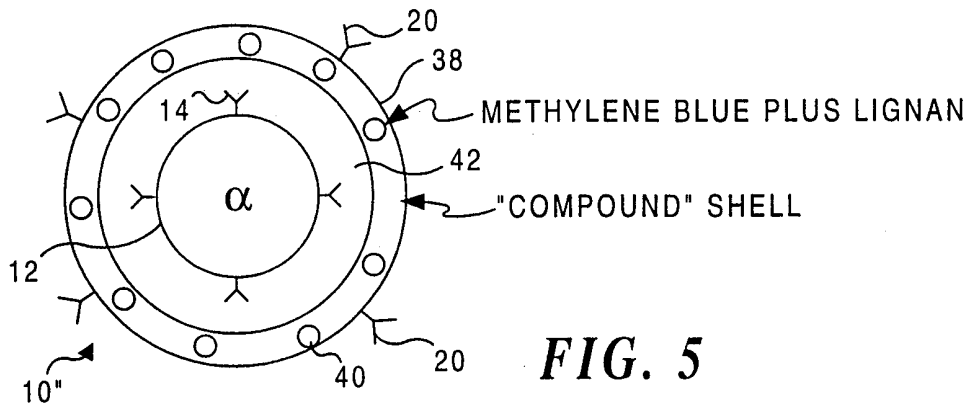

20
38
14
METHYLENE BLUE PLUS LIGNAN
42
α
"COMPOUND" SHELL
12
10"
40
20

*FIG. 5*

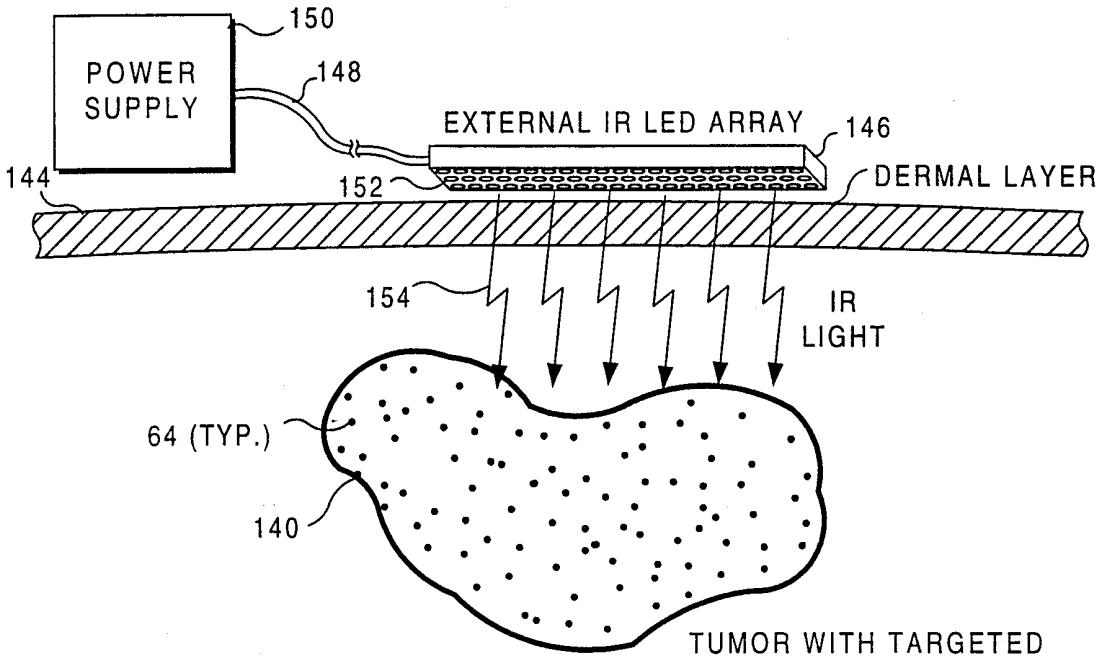

POWER SUPPLY
150
148
EXTERNAL IR LED ARRAY
146
144
152
DERMAL LAYER
154
IR LIGHT
64 (TYP.)
140
TUMOR WITH TARGETED RADIONUCLIDE BEADS LINKED TO ABNORMAL TISSUE

*FIG. 7*

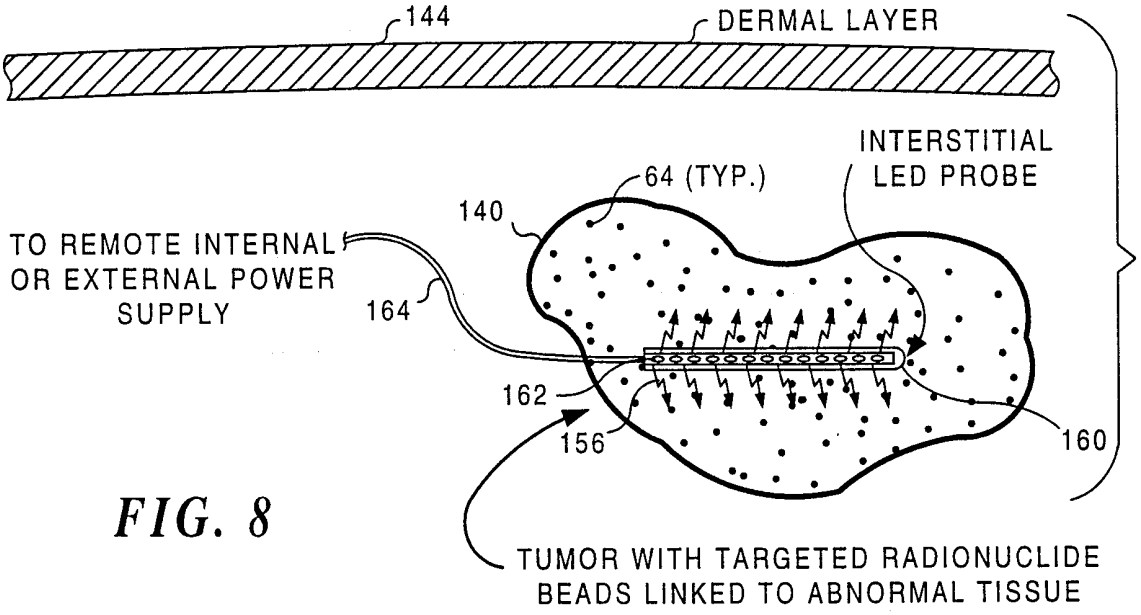

144
DERMAL LAYER
INTERSTITIAL LED PROBE
64 (TYP.)
140
TO REMOTE INTERNAL OR EXTERNAL POWER SUPPLY
164
162
156
160
TUMOR WITH TARGETED RADIONUCLIDE BEADS LINKED TO ABNORMAL TISSUE

*FIG. 8*

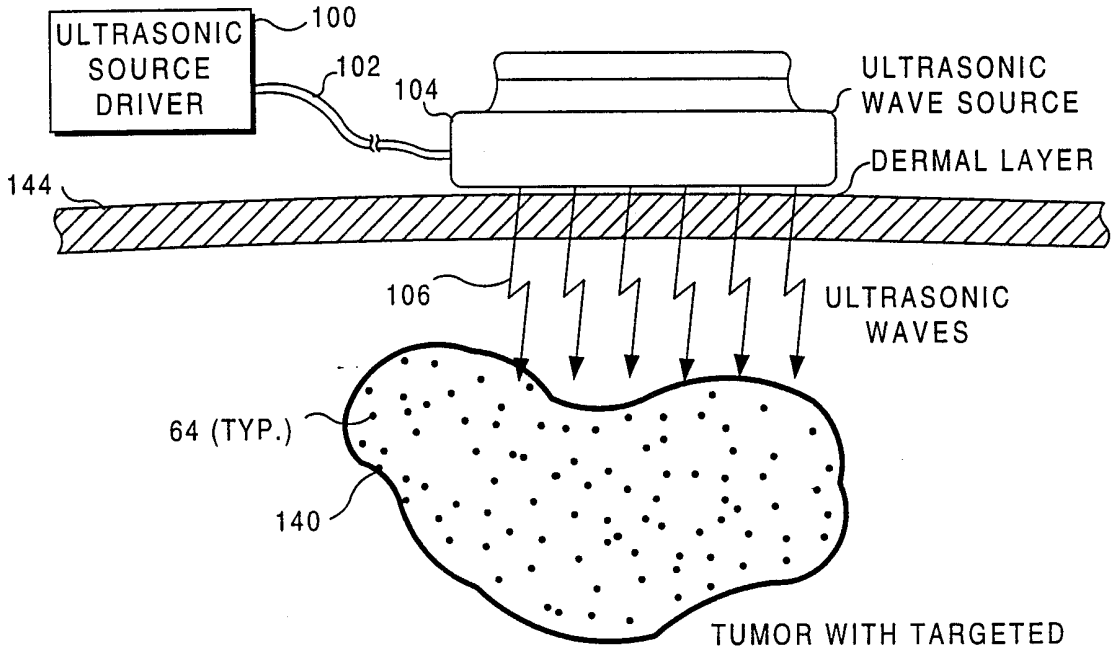

ULTRASONIC SOURCE DRIVER
100
102
104
ULTRASONIC WAVE SOURCE
DERMAL LAYER
144
106
ULTRASONIC WAVES
64 (TYP.)
140
TUMOR WITH TARGETED RADIONUCLIDE BEADS LINKED TO ABNORMAL TISSUE

*FIG. 9*

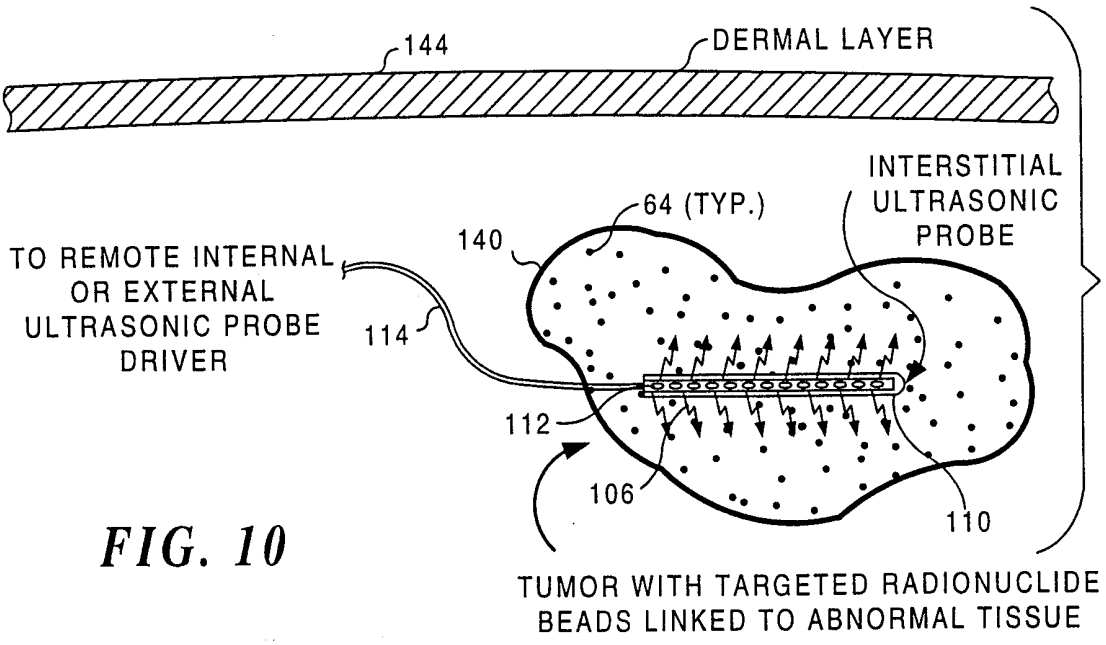

144
DERMAL LAYER
INTERSTITIAL ULTRASONIC PROBE
64 (TYP.)
140
TO REMOTE INTERNAL OR EXTERNAL ULTRASONIC PROBE DRIVER
114
112
106
110
TUMOR WITH TARGETED RADIONUCLIDE BEADS LINKED TO ABNORMAL TISSUE

*FIG. 10*

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/09584

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 41/00, 31/74, 51/00; A61N 5/00; A23L 1/28
US CL : 424/1.25, 1.33, 1.49, 1.65, 78.09, 489; 600/3

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/1.25, 1.29, 1.33, 1.49, 1.57, 1.65, 78.09, 422, 425, 426, 489; 600/1, 3, 4

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, STN, BIOSIS, MEDLINE
Search terms: radionuclei, alpha particle, beta particle, shell, microsphere, microcapsule, polymeric shell, lignan, ultrasonic

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 5,733,572 A (UNGER et al) 31 March 1998, col 35, col 36, col 57, col 58 lines 28-38. | 1-9, 11-19, 20-37 |
| X, P | US 5,770,222 A (UNGER et al) 23 June 1998, col 32 lines 43-53, col 46, col 47, col 48. | 1-9, 11-19, 20-37 |
| Y | US 4,973,465 A (BAURAIN et al) 27 November 1990, col 3, lines 44-64, col 11 lines 44-68, col 18 lines 1-68. | 1-37 |
| Y | US 5,283,255 A (LEVY et al) 01 February 1994, col 14-21. | 1-37 |

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

| | | | |
|---|---|---|---|
| * | Special categories of cited documents: | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "A" | document defining the general state of the art which is not considered to be of particular relevance | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "E" | earlier document published on or after the international filing date | "Y" | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "L" | document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "&" | document member of the same patent family |
| "O" | document referring to an oral disclosure, use, exhibition or other means | | |
| "P" | document published prior to the international filing date but later than the priority date claimed | | |

| | |
|---|---|
| Date of the actual completion of the international search | Date of mailing of the international search report<br>26 OCT 1999 |
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. | Authorized officer<br>S. Mark Clardy<br>Telephone No. 703-308-1234 |

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/09584

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | REDDI. E. et al. Liposome- or LDL-administered Zn(II)-phthalocyanine as a Photodynamic Agent for Tumours III. Effect of Cholesterol on Pharmacokinetic and Phototerapeutic Properties. Lasers in Medical Science. 1990. Vol 5. pages 339-343, especially page 340 and 342. | 1-37 |
| Y | US 5,498,421 A (GRINSTAFF et al) 12 March 1996, col 31, lines 11-67, col 39-40, col 56-58. | 1-37 |