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METHODS OF THEIR USE IN THE
DIAGNOSIS AND TREATMENT OF DISEASE**(76) Inventor: **Samuel Harry Tersigni**, Glen Allen, VA
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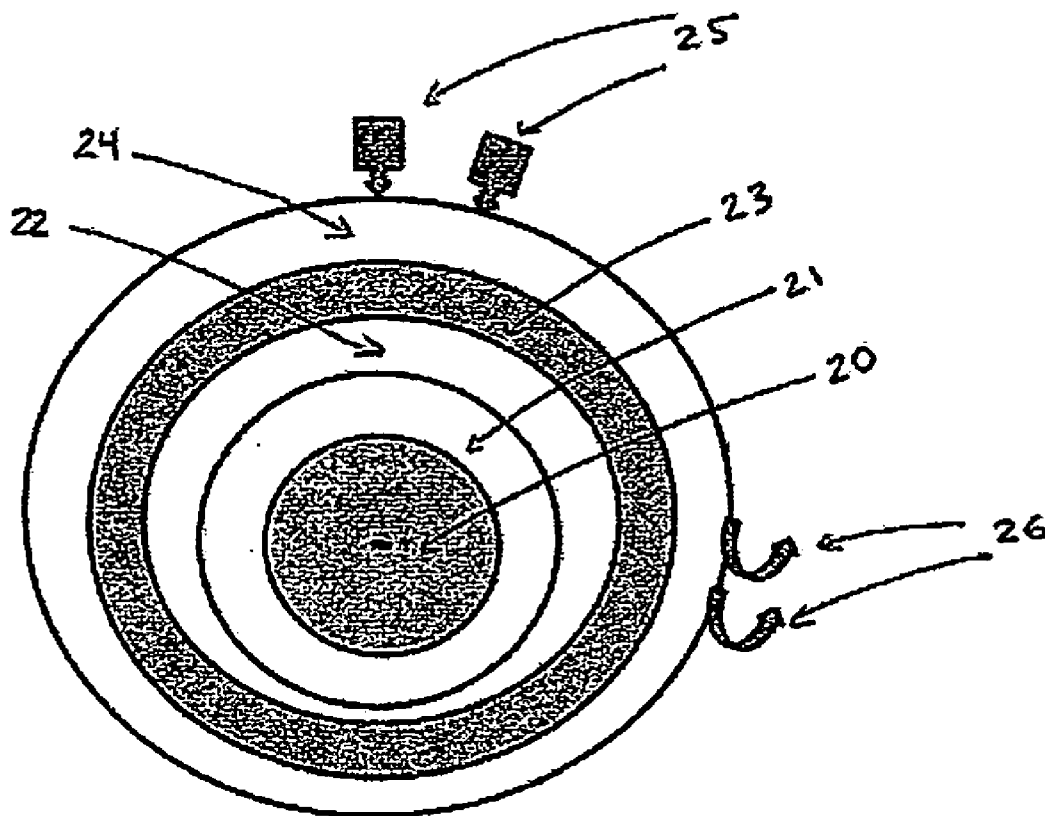
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(2), (4) Date: **Nov. 27, 2012****Related U.S. Application Data**(63) Continuation of application No. 13/052,951, filed on
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(57)

ABSTRACT

Core-excited nanoparticle thermotherapy (CENT) represents a new paradigm in thermotherapy. The CENT method employs core-shell nanoparticles. The core of the nanoparticles is formed from one or more core-exciting, energy absorbing materials which absorb core-exciting energy, either from an external energy source or from an energy source within the nanoparticle core (e.g., one or more radionuclides which undergo decay). Upon excitation by the core-exciting energy, the one or more core-exciting, energy absorbing materials reemit energy. A shell surrounds the particle nanoparticle core. The energy reemitted by the one or more core-exciting, energy absorbing materials is absorbed by the nanoparticle shell, so as to heat the shell of the nanoparticle. The heated nanoparticle then heats the surrounding region, to a temperature sufficient to detect, affect, damage or destroy the targeted cell or material. These core-shell nanoparticles can be administered to a patient in need thereof to treat diseases or disorders, including cancer. CENT nanoparticles can be optionally be bound to targeting agents that deliver them to the region of the diseased cell.



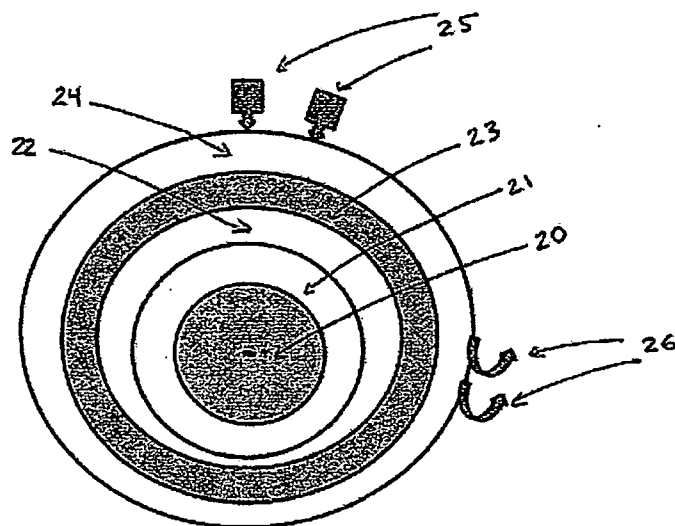


Figure 1

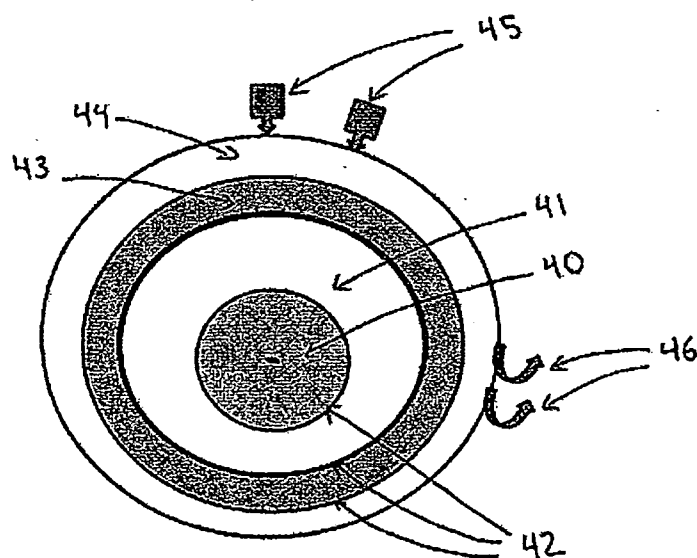


Figure 2

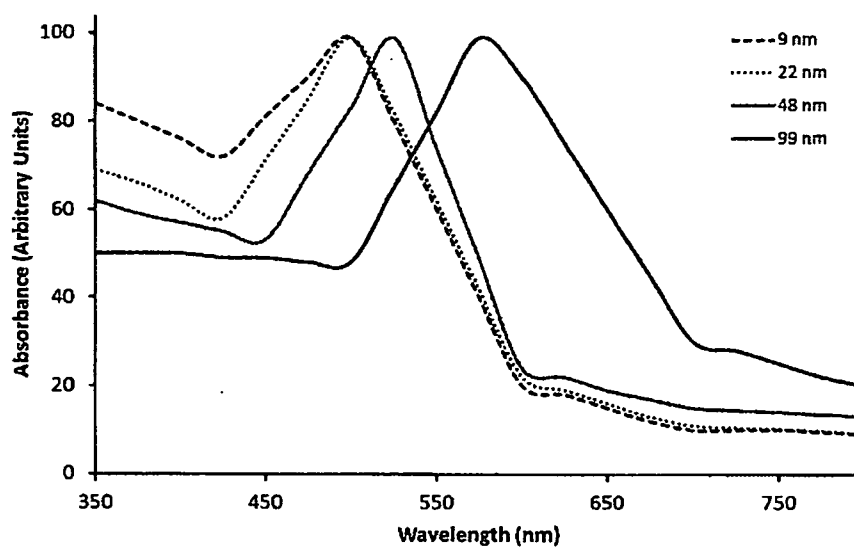


Figure 3

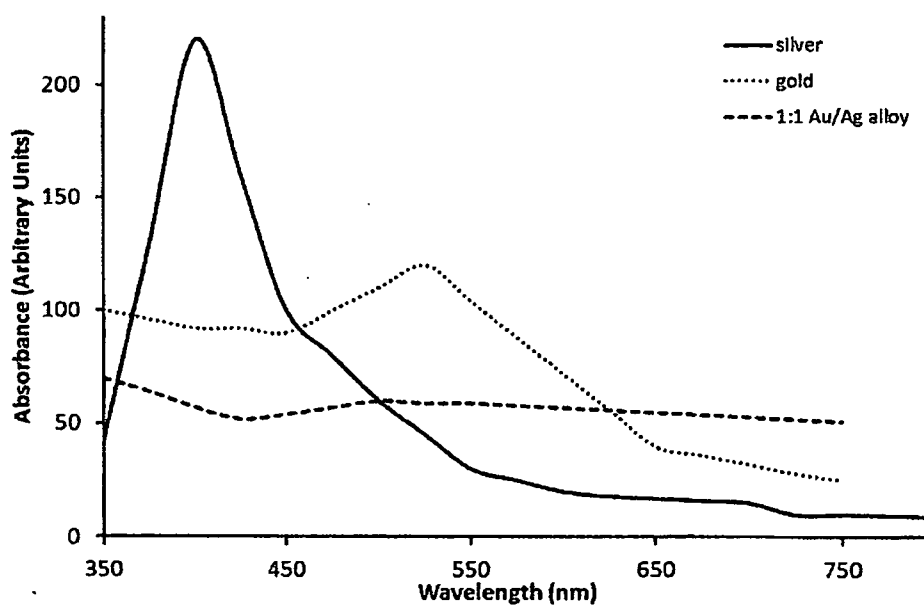


Figure 4

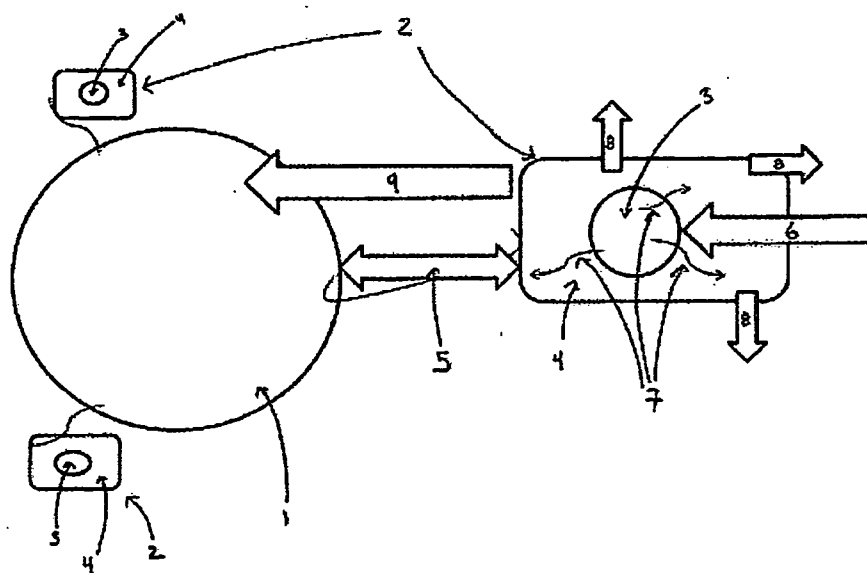


Figure 5

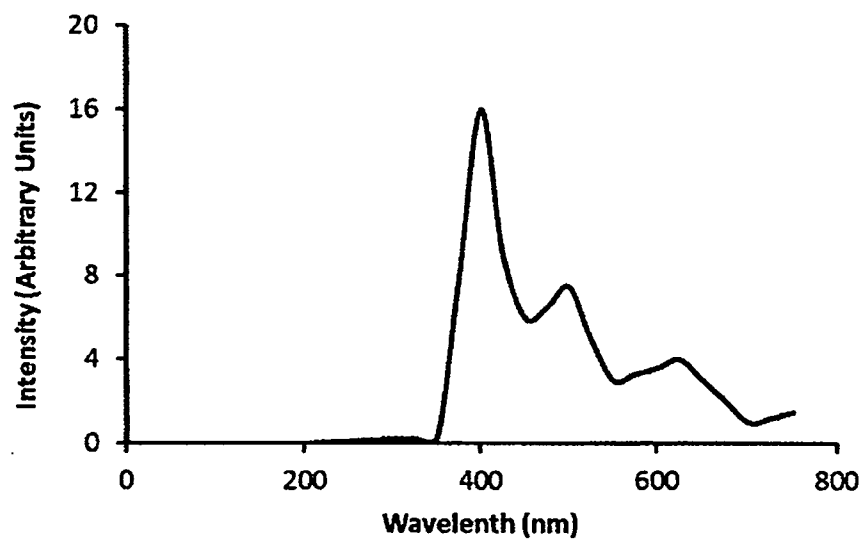
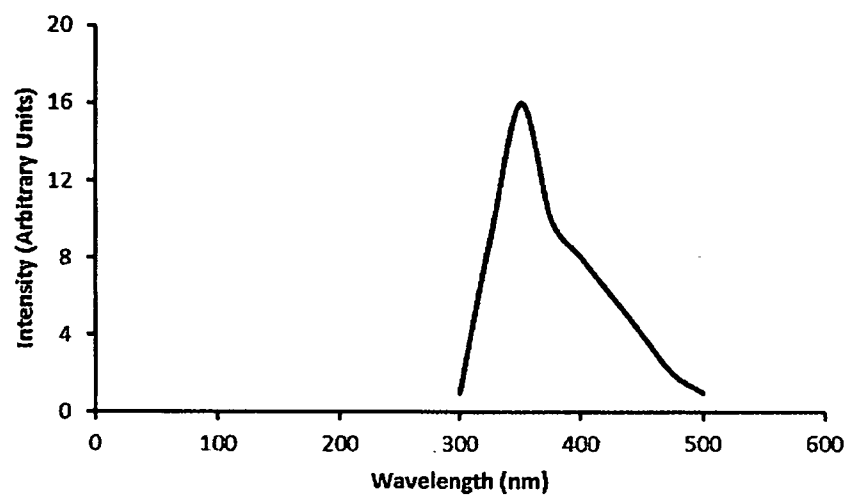
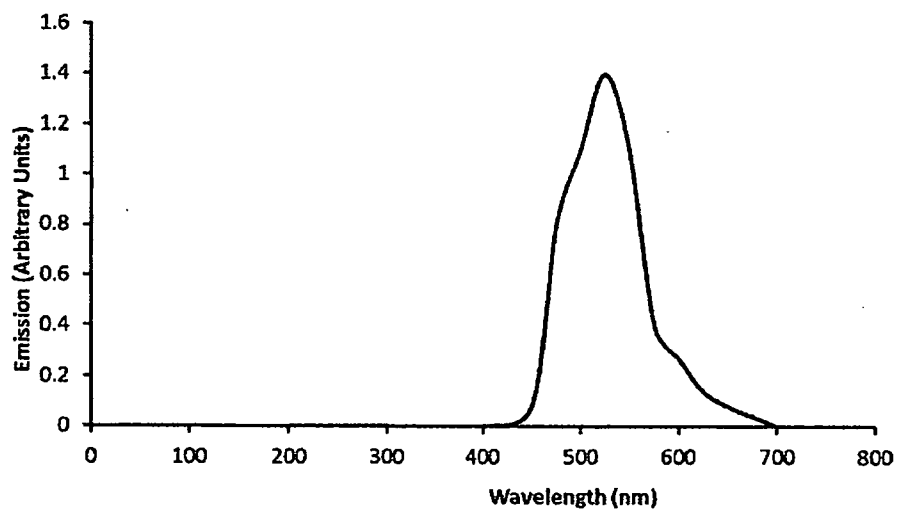


Figure 6A

**Figure 6B****Figure 7**

CORE-EXCITED NANOPARTICLES AND METHODS OF THEIR USE IN THE DIAGNOSIS AND TREATMENT OF DISEASE

FIELD OF THE INVENTION

[0001] The present invention is generally in the field of core-shell nanoparticles, especially metal and ceramic core nanoparticles, for use in diagnosis and treatment of disease.

BACKGROUND OF THE INVENTION

[0002] Generation of heat in the range of temperature from about 40° C. to about 46° C. (hyperthermia) can cause irreversible damage to diseased cells, whereas normal cells are not similarly affected. Three widely investigated methods for inducing hyperthermia, including radio-frequency waves (U.S. Pat. No. 7,510,555 to Kanzius), magnetic fields and near infrared radiation, have been utilized. As mentioned in U.S. Pat. No. 7,074,175 to Handy, “Hyperthermia may hold promise as a treatment for cancer because it induces instantaneous necrosis (typically called thermo-ablation) and/or a heat-shock response in cells (classical hyperthermia), leading to cell death via a series of biochemical changes within the cell. One particularly advantageous property is that, in some cases, heating of the local cell environment may be sufficient to kill the targeted cell but not sufficient to raise the temperature of the bulk medium.

[0003] Several laboratories have investigated cell-specific nanoparticle-based hyperthermia based on near infrared radiation (NIR). Research includes using techniques of NIR to excite gold nanoparticles and nanoshells, as described in U.S. Pat. No. 6,530,944 to West et al. In the '944 patent, after nanoparticles are delivered to a tumor or nearby cancer cells, an external NIR laser of about 800 nm in wavelength is used to excite the gold shell (plasmon mode), to generate the necessary heat. The choice and design of core material shifts the natural plasmon resonance of the gold nanoshell from the 500 nm range (of solid gold nanoparticles) to the 800 nm range. A 800 nm NIR laser is used for optimal transmission through mammalian tissue due to “water windows” for NIR. The essentially energetically inert cores of these nanomaterials in the '944 patent are made of silica and gold sulfide, neither of which absorb X-rays in any significant amount. No example in the '944 patent discusses X-rays, except with respect to the diagnostic embodiments, in which the shell is doped with scintillator material as a tag. Such technical approaches are most likely to be effective for cells in a test tube or for surface tumors of the skin. However, NIR is of limited practical clinical value for most cancers because of the inability of safe amounts of NIR to penetrate more than a few centimeters into the human body. The '944 patent also discusses the use of scintillation probes that emit IR and NIR for imaging purposes, but there is no discussion of attempts at therapeutic heat treatment with such an approach.

[0004] Other researchers have designed core-shell nanoparticles with phosphors in the core of a gold shell for the purpose of creating a sensitive diagnostic tag, enhanced by the volume of atoms that can fit inside the shell. In these cases, the shell is made to let light from the phosphor out of the shell (not to absorb it or turn it into heat), such as in the work of Kennedy and Lakshmana (International Publication No. WO 2011/084641). Specifically, these authors note that a core-shell nanoparticle “with a metal shell that does not inhibit phosphorescence from the phosphor core would further be an

advancement as it would also improve the sensitivity of the application.” These inventors design particles for medical diagnostic purposes with the view that the generation of heat is an inefficiency, stating “phosphors . . . used for the purpose of light emission, for example, produce heat and therefore the light emission efficiency is limited.”

[0005] Other researchers have designed core-shell nanoparticles to serve as diagnostic devices or to deliver focused radiation treatment. For example, Rondinone et al. (U.S. Patent Application Publication No. US 2007/0009436) uses a radioactive core inside an inorganic shell; the shell serves the purposes of i) delivering a large volume of concentrated radioactive atoms, ii) supplying a “continuous coating” so that the “ . . . radionuclide core remains undissolved when the encased radionuclide is under physiological conditions . . . ,” iii) allowing radiation to escape from the particle and iv) allowing targeting moieties to be easily attached to the particle. These particles do not generate a significant amount of heat, nor do they use shell materials that facilitate heating, as heating would suggest inefficiency in emitting radiation from these radioimmunotherapy nanoparticles.

[0006] Delivering the nanoparticle to the vicinity of the targeted cell (“targeting”) can improve therapeutic efficacy. Beyond simply injecting the nanoparticles into a region of interest, there are a wide range of targeting methodologies involving tumor cell surface molecules, including the conjugation of antibodies to various therapeutic agents and drugs. The U.S. Food & Drug Administration (FDA) has approved a number of antibody-based cancer therapeutics. In summary, there are several methods of targeting, including monoclonal antibodies (mABs) which are a practical way to carry a lethal agent specifically to the cancer cell and not to normal tissue.

[0007] While methodologies for selectively delivering nanoparticles to target cells are known, existing nanoparticles cannot be sufficiently heated to kill cells. In order to practically and effectively treat diseases and disorders using cell-specific hyperthermia, nanoparticles are needed that are capable of being selectively targeted to cells and efficiently producing thermal energy when excitation energy is applied.

[0008] It is therefore an object of the present invention to provide nanoparticles which are effective and efficient for use in hyperthermia treatment of diseases and disorders such as cancers, and which can be targeted for even greater specificity.

[0009] It is a further object of the invention to provide improved methods of treating diseases and disorders, such as cancer, using nanoparticles that are both targeted to cells and efficient at producing thermal energy when an excitation energy is applied to the particles.

SUMMARY OF THE INVENTION

[0010] Core-excited nanoparticle thermotherapy (CENT) represents a new paradigm in thermotherapy. The CENT method uses both core-excitation energy such as ionizing radiation (including X-rays) and core-shell nanoparticles, preferably formed of metal or ceramic, specifically designed to absorb such radiation in their core structure, then transfer energy from the core to the shell, to heat the shell of the nanoparticle. The heated nanoparticle then heats the surrounding region to a temperature sufficient to detect, affect, damage and/or destroy the targeted cell or material. CENT nanoparticles can be bound to targeting agents that deliver them to the region of the diseased cell.

[0011] The nanoparticles are core-shell nanoparticles formed from a core designed to absorb core-exciting energy from an energy source, and transfer the absorbed energy from the core to the shell to heat the shell of the nanoparticle. In some cases, the nanoparticles are designed to absorb core-exciting energy from an external energy source. In other embodiments, the nanoparticles further contain one or more materials within the nanoparticle which provides core-exciting energy.

[0012] Core-shell nanoparticles are formed from a core containing one or more core-exciting, energy absorbing materials. The core-exciting, energy absorbing materials absorb core-exciting energy from an energy source, and subsequently reemit energy. The energy source may be outside of the nanoparticle, such as X-ray or gamma ray radiation with an electromagnetic radiation wavelength ranging from 10.0 nm to 0.0001 nm, which may be generated from a conventional computed-tomography (CT) scanner, an X-ray or gamma-ray machine that is used in medicine, dentistry or imaging, or an X-ray laser. Alternatively, the energy source may be one or more radionuclides within the nanoparticle, most preferably within the nanoparticle core.

[0013] Examples of suitable core-exciting, energy absorbing materials include scintillators, long-lived phosphors, persistent luminescent materials, and combinations thereof. In certain embodiments, the core-exciting, energy absorbing materials are any form of strontium aluminate, such as $\text{Sr}_a\text{Al}_b\text{O}_c$, where a, b and c are integers that may vary (e.g., $\text{Sr}_4\text{Al}_{14}\text{O}_{25}$, SrAl_2O_4 , SrAl_2O_7 , and $\text{Sr}_3\text{Al}_2\text{O}_6$); any form of strontium aluminate doped with a rare earth element (RaE), $\text{Sr}_a\text{Al}_b\text{O}_c:\text{RaE}$, wherein a, b and c are integers that may vary and RaE=La, Lu, Ce, Pr, Nd, Sm, Eu, Tb, Dy, Ho, Er, Tm, or Yb in one or more oxidation states, such as Europium(II)-, Dysprosium(III)-, and Neodymium(III)-doped $\text{Sr}_4\text{Al}_{14}\text{O}_{25}$, SrAl_2O_4 , SrAl_2O_7 , and $\text{Sr}_3\text{Al}_2\text{O}_6$; any form of strontium aluminate co-doped with two or more different rare earth elements (RaEs), $\text{Sr}_a\text{Al}_b\text{O}_c:(\text{RaE})_2$, wherein a, b and c are integers that may vary and RaE=La, Lu, Ce, Pr, Nd, Sm, Eu, Tb, Dy, Ho, Er, Tm, or Yb in one or more oxidation states, such as strontium aluminate co-doped with Europium(II) and Dysprosium(III) as in $\text{Sr}_4\text{Al}_{14}\text{O}_{25}:\text{Eu}^{2+}:\text{Dy}^{3+}$, $\text{SrAl}_2\text{O}_4:\text{Eu}^{2+}:\text{Dy}^{3+}$, $\text{SrAl}_2\text{O}_7:\text{Eu}^{2+}:\text{Dy}^{3+}$, and $\text{Sr}_3\text{Al}_2\text{O}_6:\text{Eu}^{2+}:\text{Dy}^{3+}$; and strontium aluminate co-doped with Europium(II) and Neodymium(III) as in $\text{Sr}_4\text{Al}_{14}\text{O}_{25}:\text{Eu}^{2+}:\text{Nd}^{3+}$, $\text{SrAl}_2\text{O}_4:\text{Eu}^{2+}:\text{Nd}^{3+}$, $\text{SrAl}_2\text{O}_7:\text{Eu}^{2+}:\text{Nd}^{3+}$, and $\text{Sr}_3\text{Al}_2\text{O}_6:\text{Eu}^{2+}:\text{Nd}^{3+}$; any form of rare-earth ion-doped gadolinium oxide or oxysulfide phosphor, $\text{Gd}_2\text{O}_3:\text{RaE}^{3+}$ or $\text{Gd}_2\text{O}_2\text{S}:\text{RaE}^{3+}$, wherein RaE=La, Lu, Ce, Pr, Nd, Sm, Eu, Tb, Dy, Ho, Er, Tm, or Yb; any rare-earth (RaE) ion co-doped alkaline earth aluminate, $x\text{MO}+y\text{Al}_2\text{O}_3:\text{RaE}^i\text{RaE}$, where x and y are integers, and M=Ca, Sr, or Ba, and RaE=La, Lu, Ce, Pr, Nd, Sm, Eu, Tb, Dy, Ho, Er, Tm, or Yb; any rare-earth- or transition-metal-doped metal halide, including, but not limited to, $\text{LaF}_3:\text{Ce}^{3+}$, $\text{LuF}_3:\text{Ce}^{3+}$, $\text{CaF}_2:\text{Mn}^{2+}$, $\text{CaF}_2:\text{Eu}^{2+}$, $\text{BaFBr}:\text{Eu}^{2+}$, $\text{BaFBr}:\text{Mn}^{2+}$, $\text{CaPO}_4:\text{Mn}^{2+}$, $\text{LuI}_3:\text{Ce}$, $\text{SrI}_2:\text{Eu}$, $\text{CaI}_2:\text{Eu}$, $\text{GdI}_3:\text{Ce}$; or any other suitable material, such as CdS, CdSe, CdTe, CaWO_4 , ZnS:Cu, TmO, ZnSe:Te, ZnS, ZnO, TiO_2 , GaN, GaAs, GaP, InAs, InP, Y_2O_3 , WO_3 , ZrO_2 , $\text{YAlO}_3:\text{Ce}$, $\text{Y}_2\text{O}_3:\text{Eu}^{3+}$, $\text{CeMgAl}_{11}\text{O}_{19}:\text{Tb}$, $\text{LaPO}_4:\text{Ce}$, Tb, $\text{GdMgB}_5\text{O}_{10}:\text{Ce}$, Tb, $\text{BaMgAl}_{10}\text{O}_{17}:\text{Eu}^{2+}$, and $\text{Sr}_5(\text{PO}_4)_3\text{Cl}:\text{Eu}^{2+}$; and combinations thereof.

[0014] In some cases, the nanoparticles are designed to absorb core-exciting energy from an external energy source. In these cases, ionizing radiation, predominantly X-ray radiation, is applied to the nanoparticles containing a core-exciting

energy absorbing material and an energy conducting shell. However, the core must be designed to both absorb the excitation energy and then transfer the energy to heat the shell.

[0015] In certain embodiments, the one or more core-exciting, energy absorbing materials absorb photons or mass particles of individual energy of greater than about 1 eV, more preferably greater than about 60 eV, more preferably greater than about 120 eV. In preferred embodiments, the one or more core-exciting, energy absorbing materials is an X-ray absorbing species. In certain embodiments, the one or more core-exciting, energy absorbing materials absorb photons or mass particles of individual energy of between about 30 keV and 120 keV.

[0016] In the case of nanoparticles designed to absorb core-exciting energy from an external energy source, the one or more core-exciting energy absorbing species preferably possess an excited state lifetime which allows them to continue to transfer energy to the shell of the nanoparticles for some period of time after the discontinuation of excitation using an external energy source. In certain embodiments, the one or more core-exciting, energy absorbing species continue to reemit energy for more than one minute after the discontinuation of excitation by the external energy source. In this way, the shell of the nanoparticle continues to be heated for a period of time, preferably at least one minute, following the discontinuation of excitation by the external energy source.

[0017] In some embodiments, the nanoparticles further contain one or more materials which provide core-exciting energy. For example, the nanoparticle may further contain one or more radionuclides. In such cases, the primary source of energy for heating may come from the one or more radionuclides that are incorporated into the nanoparticle.

[0018] When one or more radionuclides are incorporated into the nanoparticles, the radionuclides emit decay products which excite the one or more core-exciting energy absorbing materials (e.g., scintillators). The one or more core-exciting energy absorbing materials subsequently reemit energy, preferably in the form of light in the range of 200 nm to 6000 nm.

[0019] One or more radionuclides can be incorporated into the core-shell nanoparticles in various ways. In certain embodiments, one or more radionuclides are present within the core of the core-shell nanoparticle. In these cases, the one or more radionuclides may be present as a solid mass forming an inner sphere within the core, as a layer surrounding an inner core composed of one or more core-exciting energy absorbing materials, or mixed with one or more core-exciting energy absorbing materials to form a single core structure within the nanoparticle. One or more radionuclides can also be incorporated into the shell of the core shell nanoparticles.

[0020] The one or more radionuclides may emit X-rays, gamma-rays, electrons (such as Auger electrons or Coster-Kroenig electrons), alpha particles, beta particles and other typical products of nuclear transitions. As the one or more radionuclides decay, one or more core-exciting energy absorbing materials absorb the particles emitted by the decay of the radionuclides, and emit light at a frequency that is significantly absorbed by the shell. In this way, energy is transferred from the nanoparticle core to heat the shell of the nanoparticle. For example, a cerium- and terbium-doped lanthanum phosphate (LAP) layer may absorb the decay particles of a solid inner core of Pd-103 and emit green light into a gold shell, so as to excite the surface plasmons and generate heat.

[0021] Any suitable radionuclide or radionuclides may be incorporated into the particle core. Generally, the radionuclides have a half-life, decay mode, decay energy, and combinations thereof suitable for incorporation into the core-shell nanoparticles described herein. In certain embodiments, the one or more radionuclides have half-lives of greater than about one hour and less than about fifty years, more preferably greater than about ten hours and less than about ten years, more preferably greater than about ten hours and less than about one year, most preferably greater than about one day and less than about two months.

[0022] Examples of suitable radionuclides which may be incorporated into the nanoparticles described herein include, but are not limited to, Be-7, F-18, Mg-28, P-32, P-33, S-35, Ar-37, S-35, Ca-47, Sc-46, Sc-47, V-48, Cr-51, Mn-52, Mn-54, Fe-59, Fe-55, Co-58, Co-57, Co-56, Co-55, Ni-57, Cu-67, Zn-65, Ga-67, Ge-68, Se-72, Se-75, Kr-79, Rb-83, Rb-84, Rb-86, Sr-82, Sr-83, Sr-85, Sr-89, Y-88, Y-91, Zr-95, Nb-95, Tc-95m, Tc-97m, Tc-99m, Ru-97, Ru-103, Pd-103, Pd-100, Ag-111, Cd-109, Cd-115m, In-111, In-113m, In-114m, In-115m, Sn-113, Sr-117m, Sb-119, Te-118, Te-123m, I-123, I-124, I-125, I-126, I-131, Xe-122, Xe-127, Xe-131m, Xe-133, Cs-129, Cs-131, Cs-132, Ba-128, Ba-131, Ba-140, Ce-134, Ce-139, Ce-141, Pr-143, Nd-140, Pm-149, Pm-145, Sm-145, Eu-145, Eu-147, Gd-147, Gd-149, Gd-153, Tb-157, Dy-157, Dy-159, Er-165, Er-169, Tm-167, Tm-170, Yb-169, Ta-177, Ta-179, W-178, W-181, O-191, Ir-190, Ir-192, Pt-193, Pt-193m, Pt-195m, Au-195, Hg-197, Tl-201, Tl-202, Pb-203, and combinations thereof.

[0023] The nanoparticle shell is preferably formed from one or more metals. Examples of suitable metals include gold, silver, platinum, palladium, ruthenium, rhodium, and combinations thereof, which serve as effective nanoshells for heating via plasmon absorption. The physical and optical parameters of the shell are matched to the design capabilities of the core material, as discussed below.

[0024] The core and the shell are designed to simultaneously optimize the internal molecular energy flow such that core-exciting energy absorbed in the nanoparticle core is converted to heat emission from the shell. In the case where the energy transfer between core and shell is via electromagnetic radiation, the one or more core-exciting energy absorbing materials are selected such that the emission spectrum of the one or more core-exciting energy absorbing species overlaps the absorption spectrum of the shell. In certain embodiments, one or more core-exciting energy absorbing materials which emit blue light may be combined with a silver shell which absorbs blue light. In other embodiments, one or more core-exciting energy absorbing materials which emit green light may be combined with a gold shell which absorbs green light. In other cases, an appropriately designed gold shell may be heated by red light from a scintillator such as $\text{Y}_2\text{O}_3:\text{Eu}^{3+}$. Some materials absorb high frequency ultraviolet radiation and reemit light in the visible spectrum.

[0025] In certain embodiments, the one or more core-exciting, energy absorbing materials is selected such that the energy reemitted by the one or more core-exciting energy absorbing materials following excitation by the core-exciting energy is electromagnetic radiation between about 100 nanometers and about 6000 nanometers, more preferably between about 200 nanometers and about 3000 nanometers, more preferably between 300 nanometers and 2000 nanometers.

[0026] The nanoparticles may employ chemical targeting agents to deliver them to the target cell or tissue, either in vivo or in vitro. In the preferred embodiment, the nanoparticles are bound to a targeting antibody which can further participate, either in vivo or in vitro, in antigen-antibody binding or binding to the targeted cell.

[0027] In another embodiment, heat-catalyzed functional agents (HCFAs) are bound to or associated with the nanoparticle shell or a targeting support film. HCFAs can be any therapeutic, prophylactic, or diagnostic agent which is bound to the shell or targeting support film of the nanoparticle and is released (or reacted) upon heating of the shell. In a preferred embodiment, the HCFA is an antineoplastic agent.

[0028] This technology provides practical, cost-effective methods and nanomaterial compositions for diagnosis and hyperthermia treatment of disease or disorders. The technology should be effective to treat disease that has spread throughout the body, such as metastatic cancers (known as stage IV, in the case of cancer), even when the disease is in such small amounts or locations in the body that it is not detectable. The materials and methods can also be used for imaging, with detection resulting from either the X-ray absorption or the generation of heat. The technology is practical, effective, and non-invasive, with minimal side-effects, and should be usable with existing medical hardware now widely deployed in hospitals around the world.

BRIEF DESCRIPTION OF THE DRAWINGS

[0029] FIG. 1 is a schematic cross-section (not drawn to scale) illustrating the design of nanoparticles designed to absorb external radiation in their core structure, and transfer the absorbed energy from the core to the shell to heat the outer shell of the nanoparticle.

[0030] FIG. 2 is a schematic cross-section (not drawn to scale) illustrating the design of nanoparticles containing one or more radionuclides and one or more core-exciting energy absorbing materials.

[0031] FIG. 3 is a plot of the absorbance (in arbitrary units) as a function of wavelength (in nanometers) of gold nanoparticles of different diameters (9 nm, dashed black line; 22 nm, dotted line; 48 nm, gray line, and 99 nm, black line). The maximum absorbance for the gold nanoparticles varies in a range between approximately 500 nm and 600 nm (Taken from Link and El-Sayed, J. Phys. Chem. B, 103(21):4212, 1999).

[0032] FIG. 4 is a plot of the absorbance (in arbitrary units) of metal nanoparticles (silver nanoparticles, solid black line; gold nanoparticles, dotted line; and nanoparticles formed from a 1:1 gold:silver alloy; dashed line) as a function of wavelength (in nanometers, taken from Pal et al., *African Phys. Rev.* 1 (*Special Issue—Microfluidics*) (2007)).

[0033] FIG. 5 is a schematic, not drawn to scale, describing methods of using the particles described herein for the treatment of a disease or disorder. The nanoparticles (2) contain at least a core material (3) and a shell material (4). The first step (5) involves positioning the nanoparticle(s) into the region of the targeted material (1), which may be, for example, a tissue or cell. In the case of nanoparticles designed to absorb external radiation, the next step (6) is exposing the targeted region to a source of external ionizing radiation, such as an X-ray, which the core, containing one or more core-exciting, energy absorbing materials, absorbs. In the case of nanoparticles containing one or more radionuclides, this step is not required. In these embodiments, the nanoparticle core con-

tains one or more radionuclides which decay, emitting particles that are absorbed by one or more core-exciting, energy absorbing materials located within the nanoparticle. The next step (7) involves energy transfer from the nanoparticle core material (the core-exciting, energy absorbing materials) to the nanoparticle shell for the purpose of heating the shell, through any of several mechanisms, one being overlap of the core emission spectrum with the shell absorption spectra (fluorescence resonance energy transfer, FRET). As the shell is heated, it gives off heat (8). The heat (8) is transferred from the nanoparticle shell to the nearby region that includes the targeted material (9). Optionally, in a further step not illustrated in FIG. 5, the nanoparticles may be removed from the targeted material. For example, in the case of nanoparticles administered to a patient, the nanoparticle may be removed from the patient through magnetic separation from the blood, whereby blood is taken from one arm of the patient, filtered, then returned through the other arm, in a procedure similar in clinical practice to conventional kidney dialysis.

[0034] FIGS. 6A-6B are plots of the X-ray luminescence intensity (in arbitrary units) of two nano-scintillator materials as a function of wavelength (in nanometers; taken from Chen and Zhang, *J. Nanoscience and Nanotechnology* 6, 1159-1166, 2006). FIG. 6A is a plot of the X-ray luminescence intensity of BaFBr:Eu²⁺, Mn²⁺ nanoparticles (20 nm in diameter). FIG. 6B is a plot of the X-ray luminescence intensity of LaF₃:Ce³⁺ nanoparticles (15 nm in diameter).

[0035] FIG. 7 is a plot of the X-ray emission spectrum (in arbitrary units) of Europium-activated strontium aluminate as a function of wavelength (nm). The Europium-activated strontium aluminate is 0.9 parts Strontium (Sr), 1.0 part Al₂O₃, and 0.03 parts EuO (Taken from U.S. Pat. No. 3,294,699 to Lange).

DETAILED DESCRIPTION OF THE INVENTION

[0036] The thermotherapy discussed here is for the imaging and treatment of diseases, including cancer. Hyperthermia is a long-established method of treating some diseases, but is most effective when it can be focused at the cellular or molecular level. Nanoparticles have been used to generate localized heat near a target cell, but existing methods have limitations in efficacy, cost and availability.

[0037] CENT employs core-shell nanoparticles. The core of the CENT nanoparticles is formed from a material which absorbs core-exciting energy from an energy source (e.g., one or more core-exciting, energy absorbing materials), and subsequently reemits energy. The nanoparticles are designed to absorb core-exciting energy from an external energy source, or the nanoparticles may further contain one or more materials within the nanoparticle which provides core-exciting energy. The shell, which surrounds the particle core, absorbs the energy reemitted from the one or more core-exciting energy absorbing materials, emitting heat.

[0038] In this way, the energy absorbed or generated by the core is transferred from the nanoparticle core to nanoparticle shell, so as to heat the shell of the nanoparticle. The heated nanoparticle then heats the surrounding region, to a temperature sufficient to detect, affect, damage or destroy the targeted cell or material.

[0039] CENT nanoparticles can be bound to targeting agents that deliver them to the region of the diseased cell. The method also may include the removal of nanoparticles from the body. The method also enables the imaging of targeted cells or material.

[0040] These nanoparticles provide several advantages over previously described technologies. In the case of nanoparticles designed to absorb external energy, the nanoparticles can be used in medical treatments in which the core-shell nanoparticles are exposed to X-rays for the purpose of producing therapeutic amounts of heat. In these embodiments, the nanoparticles have a core-shell configuration with a core that absorbs X-rays for the purpose of heating the shell. In many other methods of cell-specific hyperthermia, such as near infrared ("NIR"), the nanoparticle core is inert and functions primarily to shift the maximum of the (plasmon resonance) absorption spectrum of the gold shell to higher wavelength, so as to overlap with an externally applied laser, at a frequency chosen in consideration of the "water window."

[0041] In CENT, energy flows from the nanoparticle core, where core-exciting energy is absorbed, to the nanoparticle shell, which heats the targeted cells or tissue. This is in contrast to many other nanomaterials used for hyperthermia, where the plasmon resonance of the shell, which is typically gold, is directly excited by external fields, whether electric, magnetic, radiofrequency ("RF") radiation or NIR. In these instances, energy flows, if at all, from the shell to the core.

[0042] The nanoparticles can be removed from the blood if desired. CENT can be conducted using diagnostic and treatment equipment commonly found in hospitals. CENT can combine therapy and diagnostics, in that X-ray (or gamma-ray) absorption is the basis for both diagnostic tools, such as CT scans, and for treatment. CENT can be coupled with diagnostic tools, such as PET-CT scanners, to measure the efficacy of the method "in real time" and to determine the duration of the treatment session. In addition, the nanoparticle design, irradiation regime, and combinations thereof can be customized for a given disease and patient.

I. DEFINITIONS

[0043] "Core-Excited Nanoparticle Thermotherapy" (CENT), as used herein refers to a method of thermotherapy which involves the use of core-excitation energy, such as ionizing radiation, and core-shell nanoparticles, preferably formed of metal or ceramic, specifically designed to absorb such radiation in their core structure, then transfer energy from the core to the shell, to heat the shell of the nanoparticle. When core-exciting energy is applied to the nanoparticles, the nanoparticle heat the surrounding region to a temperature sufficient to detect, affect, damage and/or destroy a targeted cell or material.

[0044] "Nanoparticle," as used herein, generally refers to a particle of any shape having a diameter from about 1 nm up to, but not including, about 1 micron, more preferably from about 5 nm to about 500 nm, most preferably from about 10 nm to about 200 nm. Nanoparticles can be of any shape, such as a sphere ("nanosphere"), rod ("nanorod"), cube ("nanocube"), or ovoid ("nanoovoid").

[0045] "Core," as used herein, refers to all layers or structures forming a core-shell nanoparticle which are surrounded by or encapsulated within a shell.

[0046] "Shell," as used herein, refers to a metal or ceramic layer which surrounds the core of a core-shell nanoparticle, and is designed to be heated.

[0047] "Core-Shell Nanoparticle," as used herein, refers to a nanoparticle formed from at least two different structures (a core and a shell) formed from at least two different materials, as well as any external attachments to the shell (such as one or

more targeting agents, one or more heat-catalyzed functional agents, a targeting support film, or combinations thereof.

[0048] “Core-Exciting, Energy Absorbing Material,” as used herein, refers to a material present in the core of a core-shell nanoparticle which absorbs core-exciting energy from an energy source.

[0049] “Radionuclide,” as used herein, refers to an atom with an unstable nucleus, which is a nucleus characterized by excess energy available to be imparted either to a newly created radiation particle within the nucleus or to an atomic electron. The radionuclide, in this process, undergoes radioactive decay, and emits gamma ray(s), subatomic particles, X-rays, atomic electrons, or combinations thereof. Some of these particles constitute ionizing radiation. Radionuclides can be naturally occurring or artificially produced.

[0050] “Scintillator,” as used herein, refers to a material which luminesces when excited by radiation or particles of energy greater than 100 eV. Examples of scintillators include $\text{Y}_2\text{O}_3:\text{Eu}^{3+}$, $\text{CeMgAl}_{11}\text{O}_{19}:\text{Tb}$, $\text{La}_2\text{PO}_4:\text{Ce}$, Tb , $\text{GdMgB}_5\text{O}_{10}:\text{Ce}$, Tb^{3+} , $\text{BaMgAl}_{10}\text{O}_{17}:\text{Eu}^{2+}$, and $\text{Sr}_5(\text{PO}_4)_3\text{Cl}:\text{Eu}^{2+}$.

[0051] “Energy Source,” as used herein, refers to any form of excitation, whether from within a nanoparticle or from an external source. Examples of energy sources include radionuclides, high-energy particles and radiation from all regions of the electromagnetic spectrum; ultrasound, electric fields and magnetic fields.

[0052] “Electromagnetic Radiation,” as used herein, refers to radiation having propagating perpendicular electric and magnetic fields, and is limited to the range of radiofrequency waves through cosmic rays.

II. NANOPARTICLES AND ENERGY SOURCES FOR USE IN THERAPEUTIC METHODS

[0053] The CENT method employs core-shell nanoparticles which can be designed to either absorb energy from an external energy source or generate energy within the particle core. This energy is then transferred from the nanoparticle core to the nanoparticle shell, where heat is generated.

[0054] As described below, the mechanisms by which heat is generated between these materials determines the composition and relative amounts of the shell and core materials.

[0055] A. Core-Shell Nanoparticles

[0056] The nanoparticles described herein are formed from a core containing one or more core-exciting energy absorbing materials which absorbs core-exciting energy, and then reemits energy, and a shell surrounding, which is formed from one or more materials which absorbs the energy reemitted from the nanoparticle core, and then emits heat in sufficient quantity to kill or damage cells or tissue.

[0057] In some embodiments, the nanoparticle is a core-shell nanoparticle designed to absorb energy from an external energy source in their core structure, and transfer the absorbed energy from the core to the shell to heat the outer shell of the nanoparticle. Nanoparticles of this type are schematically illustrated in FIG. 1. The nanoparticles contain a core material (20) formed from one or more core-exciting, energy absorbing materials. The nanoparticles also contain a shell (23) formed from a material to which the energy absorbed by the one or more core-exciting, energy absorbing materials is transferred. In some embodiments, the nanoparticle can optionally contain one or more additional layers, including a core stabilizing layer (21) to improve and/or ensure particle stability, a core-shell binding layer (22) to

improve the binding between the core and the inner shell layer, and combinations thereof. Such layers are typically small, normally being less than 10 nm in thickness. The outer shell surface may need a supporting film (24), such as a polyethylene glycol (PEG) film, to allow one or more different types of targeting agents (25) to be bound to the particle surface. Heat-catalyzed functional agents (26), such as chemotherapy compounds, may also be bound to the shell or targeting support film and released (or reacted) upon heating of the shell.

[0058] In other embodiments, the nanoparticle further contains one or more materials which generate core-exciting energy within the particle core. Nanoparticles of this type are schematically illustrated in FIG. 2. The nanoparticles contain a core material (40) formed from one or more radionuclides in combination with one or more core-exciting energy absorbing materials. In some cases, the one or more radionuclides and the one or more core-exciting energy absorbing materials are mixed together, forming a single core. In these cases, the surrounding core layer (41) is not required. In preferred embodiments, the core (40) is formed from one or more radionuclides, and the core is surrounded by a layer (41) formed from one or more core-exciting energy absorbing materials (i.e., a core-exciting energy absorbing layer). In other cases, the core (40) is formed from one or more core-exciting energy absorbing materials, and the core is surrounded by a layer (41) formed from one or more radionuclides (i.e., a radionuclide layer). The nanoparticles also contain a shell (43) formed from a material to which the energy generated in the nanoparticle core is transferred. In some is embodiments, the nanoparticle can optionally contain one or more additional layers (42), including stabilizing layers to improve and/or ensure particle stability, interface binding layers to improve the binding between two adjacent layers in the nanoparticle, and combinations thereof. Such layers are typically small, normally being less than 10 nm in thickness. The outer shell surface may need a supporting film (44), such as PEG, to allow one or more different types of targeting agents (45) to be bound to the particle surface. Heat-catalyzed functional agents (46), such as chemotherapy compounds, may also be bound to the shell or targeting support film and released (or reacted) upon heating of the shell.

[0059] The nanoparticles typically have an average length or average diameter less than 1000 nm, preferably less than 500 nm, and most preferably less than 300 nm. The core material can be any diameter but is preferably less than 1000 nanometers, more preferably less than 500 nanometers. The thickness of the shell material is preferably less than 1000 nanometers, and most preferably less than 200 nanometers. In the most preferred embodiment, the nanoparticles are less than 200 nanometers, which allows them to avoid being metabolized by the liver or kidneys.

[0060] The main criteria for matching the core material to the shell material is that the radiation emission (wavelength distribution bell curve) from the core material(s) should overlap the absorption spectrum (wavelength distribution bell curve) of the shell materials, as described in more detail below.

[0061] There are several potential mechanisms of energy flow within these core-shell nanomaterials. One approach to facilitate transfer of X-ray energy within the core-shell structure is to induce core emission of radiation into the shell (FRET). There are several mechanisms of emissions from material that absorb X-rays, commonly referred to as scintil-

lator materials. These mechanisms of scintillator emission of radiation include emissions from luminescent activator ions (e.g., Ce^{3+} , Eu^{2+}), from self-trapped excitons, from excitons bound to an isoelectronic hole trap (e.g., CdS:Te), from charge-transfer emissions (e.g., CaWO_4), and from core-valence transitions (e.g., BaF_2). In scintillator materials that do not contain a luminescent ion and where a specific emission mechanism is unknown, the event is considered to be self-activated. In short, emission is just one form of energy transfer by which energy in the core material can be transferred to (absorbed by) the shell.

[0062] There are several considerations in the design of the nanoparticle shell. Along with safety, the shell may be selected to be i) transparent to X-ray or gamma-rays, ii) have a plasmon absorption spectrum that overlays the core emission (FRET), iii) be a good conductor of heat, and iv) allow attachment (if needed) of a targeting moiety and other species as needed. In the preferred embodiment, the shell comprises a significant amount of gold, silver, platinum, palladium, rhodium, ruthenium, or mixtures thereof. The plasmon absorbance spectrum of solid gold particles of about 10 nm in diameter have a maximum at around 520 nm, as indicated in FIG. 3. Silver has an absorption peak near 350-400 nm (FIG. 4). Zhou et al. have shown that modification in design of core material within a gold shell, such as adjusting the ratio of the core radius to the shell thickness (as well as the material composition of the core), can push the maximum absorbance of the gold shell into the range of 600 nm to 900 nm (Zhou, et al. *Phys. Rev. B*. 50:12052-12056 (1994)). In general, metal nanoshells have the property of having a tunable optical resonance (movable absorbance peak), which provides the opportunity to match core and shell energy to each other.

[0063] The shell and core structures must be designed as a single system. The geometric design of the core-shell structure improves energy flow from core to shell in the form of emitted radiation from the core because it minimizes energy loss due to emitted photons “missing” the shell. Almost 100% of the energy emitted is transmitted to the shell. However, if the X-ray absorbing material is placed on the shell, only a portion of the radiation emitted from this material would be emitted in the direction of the shell. Since the core-shell energy flow is within a particle, in the case of energy redistribution via intraparticle emission as discussed here (FRET), there is no need for fitting the excitation and absorbance into a “water window” (800-1300 nm and 1600-1850 nm) constraint that forces a preference for NIR over higher frequency (lower wavelength, higher energy) portions of the electromagnetic spectrum. For example, cores that emit in the visible or UV, and shells that absorb in the UV or visible, may be more preferred than NIR resonances for several reasons.

[0064] 1. Core-Exciting Energy Absorbing Materials

[0065] Core-shell nanoparticles are formed from a core containing one or more core-exciting, energy absorbing materials. The core-exciting, energy absorbing materials absorb core-exciting energy from an energy source, and subsequently reemit energy. The energy source may be outside of the nanoparticle, such as X-ray or gamma ray radiation with an electromagnetic radiation wavelength ranging from 10 nm to 0.0001 nm, which may be generated from a conventional computed-tomography (CT) scanner, an X-ray or gamma-ray machine that is used in medicine, dentistry or imaging, or an X-ray laser. Alternatively, the energy source may be one or more radionuclides within the nanoparticle.

[0066] Core-exciting energy absorbing materials may either generate intrinsic luminescence upon excitation by incident radiation or do so as a consequence of doping with ions, such as Europium, that serve the role of activators of luminescence. The incident radiation generates electron-hole pairs in the material. The relaxation of these electron-hole pairs results from a range of possible multistep mechanisms in the emission of photons in the ultraviolet, visible or near-infrared range of the spectrum. The mechanism of relaxation of ions excited by energy transfer from electron-hole pairs may involve either allowed or forbidden radiative transitions between quantized ionic or atomic energy levels. In the case of intrinsically luminescent core materials, the mechanism may involve the recombination of electron-hole pairs, radiative decay of free or trapped excitons, or core-valence transitions.

[0067] In some embodiments, the core-exciting energy absorbing materials are capable of undergoing scintillation luminescence, defined here as the reemission of electromagnetic radiation when excited by an energy source such as X-rays or gamma-rays. The nanoparticle core material can absorb energy then emits electromagnetic radiation as a result of a dopant ion, present at a minimum level to serve as an activator of luminescence. In certain embodiments, the nanoparticle core contains a material doped with at least one rare-earth- or lanthanide-series (La, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb and Lu) element of the periodic table, in an amount greater than about 0.05 mass percent of the nanoparticle, more preferably greater than about 0.1 mass percent of the nanoparticle, more preferably greater than about 0.15 mass percent of the nanoparticle.

[0068] Examples of suitable core-exciting, energy absorbing materials include scintillators, long-lived phosphors, persistent luminescent materials, and combinations thereof. In certain embodiments, the core-exciting, energy absorbing materials are any form of strontium aluminate, such as $\text{Sr}_a\text{Al}_b\text{O}_c$, where a, b and c are integers that may vary (e.g., $\text{Sr}_4\text{Al}_{14}\text{O}_{25}$, SrAl_2O_4 , SrAl_2O_7 , and $\text{Sr}_3\text{Al}_2\text{O}_6$); any form of strontium aluminate doped with a rare earth element (RaE), $\text{Sr}_a\text{Al}_b\text{O}_c:\text{RaE}$, wherein a, b and c are integers that may vary and $\text{RaE}=\text{Lu}$, La, Ce, Pr, Nd, Sm, Eu, Tb, Dy, Ho, Er, Tm, or Yb in one or more oxidation states, such as Europium(II)-, Dysprosium(III)-, and Neodymium(III)-doped $\text{Sr}_4\text{Al}_{14}\text{O}_{25}$, SrAl_2O_4 , SrAl_2O_7 , and $\text{Sr}_3\text{Al}_2\text{O}_6$; any form of strontium aluminate co-doped with two or more different rare earth elements (RaEs), $\text{Sr}_a\text{Al}_b\text{O}_c:(\text{RaE})_2$, wherein a, b and c are integers that may vary and $\text{RaE}=\text{Lu}$, La, Ce, Pr, Nd, Sm, Eu, Tb, Dy, Ho, Er, Tm, or Yb in one or more oxidation states, such as strontium aluminate co-doped with Europium(II) and Dysprosium(III) as in $\text{Sr}_4\text{Al}_{14}\text{O}_{25}:\text{Eu}^{2+}:\text{Dy}^{3+}$, $\text{SrAl}_2\text{O}_4:\text{Eu}^{2+}:\text{Dy}^{3+}$, $\text{SrAl}_2\text{O}_7:\text{Eu}^{2+}:\text{Dy}^{3+}$, and $\text{Sr}_3\text{Al}_2\text{O}_6:\text{Eu}^{2+}:\text{Dy}^{3+}$; and strontium aluminate co-doped with Europium(II) and Neodymium(III) as in $\text{Sr}_4\text{Al}_{14}\text{O}_{25}:\text{Eu}^{2+}:\text{Nd}^{3+}$, $\text{SrAl}_2\text{O}_4:\text{Eu}^{2+}:\text{Nd}^{3+}$, $\text{SrAl}_2\text{O}_7:\text{Eu}^{2+}:\text{Nd}^{3+}$, and $\text{Sr}_3\text{Al}_2\text{O}_6:\text{Eu}^{2+}:\text{Nd}^{3+}$; any form of rare-earth ion-doped gadolinium oxide or oxysulfide phosphor, $\text{Gd}_2\text{O}_3:\text{RaE}^{3+}$ or $\text{Gd}_2\text{O}_2\text{S}:\text{RaE}^{3+}$, wherein $\text{RaE}=\text{Lu}$, La, Ce, Pr, Nd, Sm, Eu, Tb, Dy, Ho, Er, Tm, or Yb; any rare-earth (RaE) ion co-doped alkaline earth aluminate, $x\text{MO}+y\text{Al}_2\text{O}_3:\text{RaE}:\text{RaE}$, where x and y are integers, and $\text{M}=\text{Ca}$, Sr, or Ba, and $\text{RaE}=\text{Lu}$, La, Ce, Pr, Nd, Sm, Eu, Tb, Dy, Ho, Er, Tm, or Yb; any rare-earth- or transition-metal-doped metal halide, including, but not limited to, $\text{LaF}_3:\text{Ce}^{3+}$, $\text{LuF}_3:\text{Ce}^{3+}$, $\text{CaF}_2:\text{Mn}^{2+}$, $\text{CaF}_2:\text{Eu}^{2+}$, BaFBrEu^{2+} , $\text{BaFBr}:\text{Mn}^{2+}$, $\text{CaPO}_4:\text{Mn}^{2+}$, $\text{LuI}_3:\text{Ce}$, $\text{SrI}_2:\text{Eu}$, $\text{CaI}_2:\text{Eu}$, $\text{GdI}_3:\text{Ce}$; or any other suitable

material, such as CdS, CdSe, CdTe, CaWO_4 , ZnS:Cu , TmO , ZnSe:Te , ZnS , ZnO , TiO_2 , GaN , GaAs , GaP , InAs , InP , Y_2O_3 , WO_3 , ZrO_2 , YAlO_3 :Ce, Y_2O_3 : Eu^{3+} , $\text{CeMgAl}_{11}\text{O}_{19}$:Tb, LaPO_4 :Ce, Tb, $\text{GdMgB}_5\text{O}_{10}$:Ce, Tb, $\text{BaMgAl}_{10}\text{O}_{17}$: Eu^{2+} , and $\text{Sr}_5(\text{PO}_4)_3\text{Cl}:\text{Eu}^{2+}$; and combinations thereof.

[0069] These materials can be made by chemical synthesis, solid state reaction, other methods, or any combination thereof. In some embodiments, the core is any form of strontium aluminate doped with Europium(II), such as $\text{Sr}_4\text{Al}_{14}\text{O}_{25}:\text{Eu}^{2+}$, $\text{SrAl}_2\text{O}_4:\text{Eu}^{2+}$, $\text{SrAl}_2\text{O}_7:\text{Eu}^{2+}$, or $\text{Sr}_3\text{Al}_2\text{O}_6:\text{Eu}^{2+}$. In some embodiments, the core is any of strontium aluminate co-doped with Europium(II) and Dysprosium(III), such as $\text{Sr}_4\text{Al}_{14}\text{O}_{25}:\text{Eu}^{2+}:\text{Dy}^{3+}$, $\text{SrAl}_2\text{O}_4:\text{Eu}^{2+}:\text{Dy}^{3+}$, $\text{SrAl}_2\text{O}_7:\text{Eu}^{2+}:\text{Dy}^{3+}$, or $\text{Sr}_3\text{Al}_2\text{O}_6:\text{Eu}^{2+}:\text{Dy}^{3+}$. In some embodiments, the core material is a semiconductor nanomaterial such as ZnS , ZnO , or TiO_2 . In preferred embodiments, the core is any form of strontium aluminate $\text{Sr}_w\text{Al}_x\text{O}_y$, doped with Eu^{2+} , Dy^{3+} , Nd^{3+} , or combinations thereof, wherein the ratio of “y/x” is from 1 to 10 and/or the ratio “w/x” is from 1 to 10 (e.g., $\text{Sr}_4\text{Al}_{14}\text{O}_{25}$, SrAl_2O_4 , SrAl_2O_7 , and $\text{Sr}_3\text{Al}_2\text{O}_6$ doped with Eu^{2+} , Dy^{3+} , Nd^{3+} , or combinations thereof).

[0070] In certain preferred embodiments, the one or more core-exciting energy absorbing materials are AlO_3 :Ce, Y_2O_3 : Eu^{3+} , $\text{CeMgAl}_{11}\text{O}_{19}$:Tb, LaPO_4 :Ce, Tb, $\text{GdMgB}_5\text{O}_{10}$:Ce, Tb, $\text{BaMgAl}_{10}\text{O}_{17}$: Eu^{2+} , $\text{Sr}_5(\text{PO}_4)_3\text{Cl}:\text{Eu}^{2+}$, or combinations thereof.

[0071] In certain embodiments, the one or more core-exciting, energy absorbing materials absorbs a significant amount of photons or mass particles of individual energy of greater than about 1 eV, more preferably greater than about 6 eV, more preferably greater than about 60 eV, more preferably greater than about 120 eV, more preferably greater than about 500 eV, more preferably greater than about 1 keV, more preferably greater than about 30 keV. In preferred embodiments, the one or more core-exciting, energy absorbing materials is an X-ray absorbing species. In certain embodiments, the one or more core-exciting, energy absorbing materials absorbs photons or mass particles of individual energy of between about 30 keV and 120 keV.

[0072] In the case of nanoparticles designed to absorb core exciting energy from an external energy source, the one or more core-exciting energy absorbing species preferably possess an excited state lifetime which allows them to continue to transfer energy to the shell of the nanoparticles for some period of time after the discontinuation of excitation using an external energy source. In certain embodiments, the one or more core-exciting, energy absorbing species continue to reemit energy for more than one minute after the discontinuation of excitation by the external energy source. In this way, the shell of the nanoparticle continues to be heated for a period of time, preferably at least one minute, following the discontinuation of excitation by the external energy source.

[0073] In certain embodiments, the one or more core-exciting, energy absorbing materials is selected such that the energy reemitted by the one or more core-exciting energy absorbing materials following excitation by the core-exciting energy is electromagnetic radiation between about 100 nanometers and about 6000 nanometers, more preferably between about 200 nanometers and about 3000 nanometers, more preferably between about 250 nanometers and about 3000 nanometers, more preferably between 300 nanometers and 2000 nanometers, more preferably between 300 nanometers and 1000 nanometers.

[0074] 2. Radionuclides

[0075] In some embodiments, the nanoparticles further contain one or more materials within the nanoparticle which provides core-exciting energy. In certain embodiments, the nanoparticle may further contain one or more radionuclides. In such cases, the primary source of energy for heating may come from the one or more radionuclides that are incorporated into the nanoparticle.

[0076] One or more radionuclides can be incorporated into the core-shell nanoparticles in various ways. In certain embodiments, one or more radionuclides are present within the core of the core-shell nanoparticle. In these cases, the one or more radionuclides may be present as a solid mass forming an inner sphere within the core, as a layer surrounding an inner core composed of one or more core-exciting energy absorbing materials, or mixed with one or more core-exciting energy absorbing materials to form a single core structure within the nanoparticle. One or more radionuclides can also be incorporated into the shell of the core shell nanoparticles. In these embodiments, the one or more radionuclides in the nanoparticle shell may both excite the one or more core-exciting energy absorbing materials and affect the target cells or tissue.

[0077] In the case of nanoparticles containing both a radionuclide and a core-exciting energy absorbing material, it is important to realize that both these components and the shell material must all be designed together. In these systems, energy flows 1) from the radionuclide to the core-exciting energy absorbing material, in the form of radionuclide decay particles which are absorbed by the core-exciting energy absorbing material (e.g., a scintillator), 2) from the core-exciting energy absorbing material to the shell, in the form of electromagnetic radiation emitted by the core-exciting energy absorbing material and absorbed by the shell to produce heat (from surface plasmon modes excited by visible light), and 3) heat from the shell to the nearby targeted elements. For example, a cerium- and terbium-doped lanthanum phosphate (LAP) layer may absorb the decay particles of a solid inner core of Pd-103 and emit green light into a gold shell, so as to excite the surface plasmons and generate heat.

[0078] The one or more radionuclides may emit particles, such as alpha particles, beta particles, X-rays, gamma-rays, atomic electrons, Coster-Kronig electrons, Auger electrons, neutrons, and combinations thereof. One or more of the core-exciting energy absorbing materials described above, absorb the particles emitted by the decay of the radionuclide, and emit light at a frequency that is significantly absorbed by the shell. In this way, energy is transferred from the nanoparticle core to heat the shell of the nanoparticle.

[0079] Any suitable radionuclide or radionuclides may be incorporated into the nanoparticle. Generally, the radionuclides have a half-life, decay mode, decay energy, and combinations thereof suitable for incorporation into the core-shell nanoparticles described herein. In certain embodiments, the one or more radionuclides have half-lives of greater than about one hour and less than about fifty years, more preferably greater than about one hour and less than about ten years, more preferably greater than about ten hours and less than about one year, most preferably greater than about one day and less than about two months.

[0080] Examples of suitable radionuclides which may be incorporated into the nanoparticles described herein include Be-7, F-18, Mg-28, P-32, P-33, S-35, Ar-37, S-35, Ca-47, Sc-46, Sc-47, V-48, Cr-51, Mn-52, Mn-54, Fe-59, Fe-55, Co-58, Co-57, Co-56, Co-55, Ni-57, Cu-67, Zn-65, Ga-67,

Ge-68, Se-72, Se-75, Kr-79, Rb-83, Rb-84, Rb-86, Sr-82, Sr-83, Sr-85, Sr-89, Y-88, Y-91, Zr-95, Nb-95, Tc-95m, Tc-97m, Tc-99m, Ru-97, Ru-103, Pd-103, Pd-100, Ag-111, Cd-109, Cd-115m, In-111, In-113m, In-114m, In-115m, Sn-113, Sn-117m, Sb-119, Te-118, Te-123m, I-123, I-124, I-125, I-126, I-131, Xe-122, Xe-127, Xe-131m, Xe-133, Cs-129, Cs-131, Cs-132, Ba-128, Ba-131, Ba-140, Ce-134, Ce-139, Ce-141, Pr-143, Nd-140, Pm-149, Pm-145, Sm-145, Eu-145, Eu-147, Gd-147, Gd-149, Gd-153, Tb-157, Dy-157, Dy-159, Er-165, Er-169, Tm-167, Tm-170, Yb-169, Ta-177, Ta-179, W-178, W-181, O-191, Ir-190, Ir-192, Pt-193, Pt-193m, Pt-195m, Au-195, Hg-197, Tl-201, Tl-202, Pb-203, and combinations thereof.

[0081] 3. Shell Materials

[0082] The nanoparticle shell is preferably formed from one or more metals; however, ceramics which possess surface plasmon modes can also be used. Examples of suitable metals include gold, silver, platinum, palladium, rhodium, ruthenium, and combinations thereof, which serve as effective nanoshells for heating via plasmon absorption. Ceramic semi-conductors materials, such as ZnO and TiO₂, are also potentially useful because of their plasmonic modes. The physical and optical parameters of the shell are matched to the design capabilities of the core material, as discussed below.

[0083] The core and the shell are designed to simultaneously optimize the internal molecular energy flow such that core-exciting energy absorbed in the nanoparticle core is converted to heat emission from the shell. In the case where the energy transfer between core and shell is via electromagnetic radiation, the one or more core-exciting energy absorbing materials are selected such that the emission spectrum of the one or more core-exciting energy absorbing species overlaps the absorption spectrum of the shell. In certain embodiments, one or more core-exciting energy absorbing materials which emit blue light may be combined with a silver shell which absorbs blue light. In other embodiments, one or more core-exciting energy absorbing materials which emit green light may be combined with a gold shell which absorbs green light.

[0084] 4. Additional Layers within the Nanoparticles

[0085] In addition to the core and shell, the nanoparticle described above can optionally contain one or more additional layers. In some embodiments, the nanoparticle core is surrounded by or has integrated into a core stabilizer (e.g., a film or covering layer to ensure the hydrolytic stability of the core). In some embodiments, the nanoparticle contains a core-shell binder (e.g., a film or layer between the nanoparticle core and shell or between layers of the core that facilitates binding of the core layers and/or the core to the inner layer of the nanoparticle shell). Non-limiting examples of such films include phosphates and amines. In some embodiments, the shell of the nanoparticle is coated with a targeting support film (e.g., polyethylene glycol) which serves as a point of attachment for targeting ligands and/or HCFAs. Additional particle layers are typically small, normally less than 10 nm in thickness, and are introduced into the particle without causing significant detriment to energy flow between the core and shell.

[0086] B. Energy Sources and Particle Design

[0087] The nanoparticles can be excited by any suitable energy source, including radionuclides, high-energy particles and radiation from all regions of the electromagnetic spectrum; ultrasound, electric fields and magnetic fields. Such sources can be used in exciting atoms, molecules, chemical

complexes, composite particles or nanomaterials. The term "exposure" herein means an irradiation regime, for either diagnostic or therapeutic purposes, that may include i) single events or multiple events, ii) in one session or many sessions over many years, or iii) involve a single particle or photon or a wide spectral range of photons.

[0088] In certain embodiments, the energy source is an X-ray. A suitable X-ray is any electromagnetic radiation that is sufficient to pierce the human body; preferable X-rays are those with wavelengths less than 10 nanometers, more preferably those with wavelengths between 10.0 and 0.001 nanometers. The power and pulsing of the X-ray must be sufficient to bring about the desired heating of the target cell, which may vary among diseases and patients. X-ray devices that may be used in the methods herein include conventional commercial X-ray units commonly used for diagnostic or therapeutic purposes, computed-tomography (CT) scanners, full-body scanners or even X-ray lasers. X-rays may be products of radionuclide decay.

[0089] X-rays are advantageous because of both their ability to penetrate through the entire body and the amount of energy contained within the X-ray photon. But other high-energy sources, such as gamma rays, and high-energy particles can also be used. The core material of the nanoparticle should be chosen to both absorb the energy and then direct the energy flow into exciting a heating mode of the shell so as to generate heat.

[0090] In certain embodiments, the energy source is a gamma ray. A suitable range of gamma-ray radiation is an amount sufficient to pierce the human body and excite the nanoparticle core material, to begin step 2 of the process, as outlined in FIG. 5. Electromagnetic radiation in the wavelength range of 0.01 to 0.00001 nm is typically considered gamma radiation.

[0091] In some cases, the energy source is a high energy particle. High-energy particles include positrons, such as those used in positron emission tomography (PET) scans, and high-energy protons and electrons and are useful as sources of energy.

[0092] As described above, the energy source for particle heating can also be one or more radionuclides incorporated within the nanoparticles. Radionuclides are atoms with unstable nuclei, which are nuclei characterized by excess energy available to be imparted either to a newly created radiation particle within the nucleus or to an atomic electron. Radionuclides undergo radioactive decay, emitting gamma ray(s), X-rays, subatomic particles, or combinations thereof. Some of these particles constitute ionizing radiation. Radionuclides occur naturally, and can also be artificially produced. Many types of high-energy particles can be emitted from radionuclides, including those discussed below. Alpha particles are charged particles with mass and charge equal to a helium nucleus, which consists of two protons and two neutrons but no electrons. A beta particle is a negatively or positively charged electron (negatron or positron) that is emitted from the nucleus, simultaneously with a neutrino. Coster-Kroenig and Auger electrons are atomic electrons that are emitted from the atom as a result of a transitions occurring within the K- and L-shells of the atom. Neutrons are located in the nucleus and have mass similar to that of a proton but carry no charge.

[0093] Ionizing radiation consists of particles or electromagnetic waves that are energetic enough to detach electrons from atoms or molecules, thereby ionizing them. Direct ion-

ization from the effects of single particles or single photons produces free radicals, which are atoms or molecules containing unpaired electrons, that tend to be especially chemically reactive due to their electronic structure. The degree and nature of such ionization depends on the energy of the individual particles (including photons), not on their number (intensity). In the absence of heating or multiple absorption of photons, an intense flood of particles or particle-waves will not cause ionization if each particle or particle-wave does not carry enough individual energy to be ionizing (e.g., a high-powered radio beam). Conversely, even very low-intensity radiation will ionize, if the individual particles carry enough energy (e.g., a low-powered X-ray beam). Roughly speaking, particles or photons with energies above a few electron volts (eV) are ionizing, no matter what their intensity. Examples of ionizing particles are alpha particles, beta particles, neutrons, and cosmic rays. The ability of an electromagnetic wave (photons) to ionize an atom or molecule depends on its frequency, which determines the energy of its associated particle, the photon. Radiation from the short-wavelength end of the electromagnetic spectrum, high-frequency ultraviolet, X-rays, and gamma rays, is ionizing, due to their composition of high-energy photons. Lower-energy radiation, such as visible light, infrared, microwaves, and radio waves, are not ionizing.

[0094] A scintillator is a material which exhibits the property of luminescence when excited by ionizing radiation. Luminescent materials, when struck by an incoming particle, absorb its energy and scintillate, i.e., reemit the absorbed energy in the form of a small flash of light, typically in the visible range. If the reemission occurs promptly, i.e., within the approximately 10^{-8} s required for an atomic transition, the process is called fluorescence. Sometimes, the excited state is metastable, so the relaxation back out of the excited state is delayed, necessitating anywhere from a few microseconds to hours depending on the material. The process then corresponds to either one of two phenomena, depending on the type of transition and hence the wavelength of the emitted optical photon: delayed fluorescence or phosphorescence (also called after-glow). In order to supply a source of continuous heating of the targeted material to induce hyperthermia, delayed fluorescence and phosphorescence offer the ability for continued heating of the nanoparticle shell from the inside. A third approach is to use a sequence of high luminosity X-ray scintillations.

[0095] In embodiments that employ external X-rays, there are two basic approaches to the design of the core-shell nanoparticle if FRET is the method of intraparticle energy flow from the core to the shell. The first approach is to use high luminosity materials that emit large amounts of energy, but only for a short time after the excitation pulse (here the X-ray) is terminated. Repeated pulses of X-ray excitation are required for shell heating. The second approach is to use materials that emit for much longer periods of time but at a lower intensity. More than one excitation dose of (X-ray) radiation may be necessary and applied. Within the core material, the energy depth of electron traps, and the number of electron traps, in the nanomaterial are the main factors in designing a nanomaterial with long and intense afterglow performance. (Chang et al. *J. of Alloys and Compounds*; 415:220-224 (2006)).

[0096] For some diseases, a less rapid elevation in temperature, along with a less elevated temperature level that is sustained over longer time periods, offers more selective destruc-

tion of targeted cells, than does rapid high-powered heating. Therefore, the CENT treatment paradigm includes nanoparticle designs and irradiation schemes that cover the extremes of treatment approaches, from rapid heating and destruction of targeted species (seconds) to much longer periods (days) of continuous therapeutic heating by CENT nanoparticles.

[0097] In the first approach above, the nanoparticle core is made from high luminosity scintillation material, which is then subjected to a series of X-ray pulses over time to heat the nanoshell. X-ray excited scintillation luminescence is the common term given to this excitation. Moses et al., IEEE Trans. Nucl. Sci., NS-45, 462, 1998, discuss dense infrared emitting scintillators. The infrared (and NIR) radiation band is just one portion of the electromagnetic spectrum that can be used, but is useful as an example because of the data summarized in Table 1. More specifically, in Tables 1 and 2 of the Moses et al. publication, the authors note that rare earth elements and other specific ions, when used as dopants into the proper host material, can have intense room temperature luminescent emissions in the 200-1100 nm range. The website <http://scintillator.lbl.gov> lists scintillator properties, from which Table 1 below was constructed. The first entry in Table 2 is of LuI_3 , doped with Ce. The mechanism of scintillation is based on the Ce^{3+} ion. This material has high luminosity in that 98,000 photons at 540 nm (visible) are emitted for every MeV of X-ray energy that is absorbed; but the emission is relatively long for scintillation (a duration of 10 microseconds). The binding of this material within a gold or silver shell is guided by the reported synthesis of a hybrid nanoparticle of AgI and gold (Au), (*J. Phys. Chem.* 104, 4031 (2000)), offering evidence of metal iodides binding with gold.

TABLE 1

X-ray Excitation of High Luminosity Scintillation Materials				
Formula	Mechanism	Photons/ MeV Luminosity	Emission duration (nanoseconds, ns)	Emission Peak (nanometers)
$\text{LuI}_3\text{:Ce}$	Ce^{3+}	98,000	10 microseconds	540 nm
$\text{SrI}_2\text{:Eu}$	Eu^{2+}	120,000	1200 ns	435 nm
$\text{CaI}_2\text{:Eu}$	Eu^{2+}	86,000	790 ns	470 nm
$\text{GdI}_3\text{:Ce}$	Ce^{3+}	89,000	33 ns	563 nm

[0098] U.S. Pat. No. 4,499,005 to McColl et al. discloses the use of thulium (Tm), along with silver coactivated zinc sulfide in an infrared-emitting phosphor that emits at 800 nm. This finding is in agreement with that reported in Moses et al., where the Tm^{+3} ion transitions of $^3\text{H}_4 \rightarrow ^3\text{H}_6$ and $^1\text{G}_4 \rightarrow ^3\text{H}_5$ correspond to 800 nm when the Tm^{+3} powders of $\text{YPO}_4\text{:2\% Tm}$ and $\text{LuPO}_4\text{:2\% Tm}$, were excited with X-rays in the 20-30 KeV range. The $\text{YPO}_4\text{:2\% Tm}$ material was reported to yield 9242 photons/MeV (this value may be high due to the nature of the powdered sample). Importantly, rare-earth-based materials can be used to form nanorods, as demonstrated by Das et al., *Langmuir*, 26(11):8959 (2010), and references therein. As shown in FIG. 5 of the Das et al. publication, significant luminescence in the 500-700 nm range occurs upon excitation of nanorods of Yb/Er-co-doped Gd_2O_3 .

[0099] In the above second approach to designing the desired CENT nanoparticles, the nanoparticle core is made from long-lived luminescence material, employing X-ray (or gamma ray) excited persistent luminescence, the basic mechanisms of which are either delayed fluorescence or

phosphorescence (also known as long-lived phosphors or after glow). Select members of these classes of materials absorb high energy X-rays and then emit radiation in a spectral range that overlaps the absorption spectrum of important metal nanoshells, including gold. As an example, FIG. 6A shows the X-ray luminescence spectrum of BaFBr:Eu²⁺, Mn²⁺ nanoparticles, while FIG. 6B shows the similar spectrum of LaF₃:Ce³⁺. These emission spectra overlap the absorption spectra of gold nanoshells (FIG. 3). BaFBr:Eu²⁺ and Mn²⁺ and LaF₃:Ce³⁺ nanoparticles, designed with a “trap system” to sustain luminescence, can emit light with an intensity exceeding 25 mW/cm² (Chen and Zhang, *J. Nanoscience and Nanotechnology* 6, 1159-1166, 2006). Strontium aluminate (SrAl₂O₄) has also been recognized as a long-lived phosphor. Europium (Eu²⁺) doped versions of SrAl₂O₄ are also well known as a further enhancement. More recent enhancements include co-doping with Eu²⁺ and Dy³⁺ for long “after-glow” duration, which are available commercially (see Table 2 below).

TABLE 2

Select Commercial Long-lived (afterglow) Phosphors			
Supplier nm	Product Composition	Emission Time	Emission Peak
MolTECH GmbH	SrAlO ₄ :Eu, Dy	15-18 hours	530 nm
MolTech GmbH	CaAlO ₄ :EuDy	8-10 hours	440 nm
Boston ATI	SrAl ₂ O ₄ :Eu	10 hours	525 nm
Boston ATI	Sr ₄ Al ₁₄ O ₂₅ :Eu	10 hours	490 nm

[0100] Therefore, persistent luminescence from a nanoparticle core can supply the total energy needed to supply a lethal level of heat to tumor cells. In comparison to the total energy deposited into the gold nanoshells proven effective for NIR ablation of human colorectal tumors in mice, as suggested by the entries in Table 1, a core emission of 25 mW/cm² for a period of 7 hours is necessary. The implicit assumption in this calculation is that the skin of the nude mice is transparent to the 800 nm NIR, just as one assumes that the transfer from the CENT core to the shell is 100% efficient.

[0101] Photodynamic therapy (PDT) is a therapeutic approach to disease, including cancer, whereby singlet oxygen is generated in vivo (or in vitro) by light. Singlet oxygen then plays a central role in the attack on the cancer cell. Scintillation and persistent luminescent materials are two classes of materials of research interest in PDT, that have X-ray excited emission in the 350 nm to 750 nm range with long lifetimes. Researchers in PDT have worked with long-lived luminescence, but their application is not related to thermotherapy, nor do they consider coating their nanoparticles with a metal shell. As expected by their need for visible light, the nanomaterials discussed in PDT research literature employ an emission spectrum that could be made to overlap the absorption spectrum needed to heat gold (or silver) nanoshells. Also importantly, these scintillation and persistent luminescent materials have been shown to be useful for fabrication into nanoparticles for use in the generation of singlet oxygen for PDT. (Chen and Zhang, *J. Nanoscience and Nanotechnology* 6, 1159-1166, 2006).

[0102] C. Targeting Molecules

[0103] Systemically administered nanoparticles may be targeted so that they travel to a desired location where they are retained until activated by an energy source. They may also be sized so that they are administered to an area and then retained

as the nanoparticles are trapped within smaller blood or lymph vessels into the tissue. A targeting molecule is a substance which will direct the particle to a receptor site on a selected cell or tissue type, can serve as an attachment molecule, or serve to couple or attach another molecule. As used herein, “direct” refers to causing a molecule to preferentially attach to a selected cell or tissue type. This can be used to direct cellular materials, molecules, or drugs, as discussed below.

[0104] Targeting ligands include any molecule that recognizes and binds to target antigen or receptors over-expressed or selectively expressed by particular cells or tissue components. These may include antibodies or their fragments, peptides, glycoproteins, carbohydrates or synthetic polymers. Specificity is determined through the selection of the targeting molecules. The effect can also be modulated through the density and means of attachment, whether covalent or ionic, direct or via the means of linkers. Targeted particles which have therapeutic compounds such as drugs, cellular materials or components, and antigens, and have targeting ligands directly bound to the particle surface can be used to induce cellular immunologic responses or as therapeutics. Targeting greatly increases specificity, while not decreasing therapeutic load, such as DNA vaccines, drugs, peptides proteins or antigens. Another advantage is that more than one material can be encapsulated and/or coupled to the surface of the particle. This may be a therapeutic and/or targeting material.

[0105] Targeting molecules can be proteins, peptides, nucleic acid molecules, saccharides or polysaccharides that bind to a receptor or other molecule on the surface of a targeted cell. The degree of specificity can be modulated through the selection of the targeting molecule. For example, antibodies are very specific. These can be polyclonal, monoclonal, fragments, recombinant, or single chain, many of which are commercially available or readily obtained using standard techniques. Antibodies, peptides and aptamers are just a few ways of identifying and selectively binding to both nanoparticles and tumor cells. For example, the cell-surface differentiation antigen A33 is a glycoprotein that is expressed in greater than 95% of primary and metastatic colon cancer cells, but absent in normal cells. (US 2009/0263394 A1 by Scanlan et al.) Antibodies developed against the A33 antigen bind to tumor cells and exhibit prolonged retention in tumor tissue. A mouse monoclonal antibody (mAb), and a humanized version (huA33), have been developed and radio-labeled for studies. These antibodies can be attached to a gold metal surface through use of a polyethylene glycol (PEG) derivative. An excellent review of targeting molecules and nanoparticles to tumors is by Ruoslahti, *Nat. Rev. Cancer*, 2:83-90, 2002. For breast cancer, the recombinant humanized monoclonal antibody trastuzumab (mAb-trz) has seen most use as an imaging agent, when labeled with the radioisotope zirconium Zr 89, with radioisotopic activity. The trastuzumab moiety of zirconium Zr 89 trastuzumab binds with high affinity to the extracellular domain of human epidermal growth factor receptor 2 (HER2). Upon binding, the radioisotope moiety can be used in positron emission tomography (PET), allowing the imaging and quantification of HER2-expressing tumor cells. HER2, a tyrosine kinase client protein of heat shock protein 90 (Hsp90), may be over expressed on the cell surfaces of various tumor cell types; most current research on mAb-trz involves breast cancer.

[0106] Examples of molecules targeting extracellular matrix (“ECM”) include glycosaminoglycan (“GAG”) and collagen.

[0107] Nanoparticles may be treated using a mannose amine. This treatment may cause the nanoparticles to bind to the target cell or tissue at a mannose receptor on the antigen presenting cell surface. Alternatively, surface conjugation with an immunoglobulin molecule containing an Fc portion (targeting Fc receptor), heat shock protein moiety (HSP receptor), phosphatidylserine (scavenger receptors), and lipopolysaccharide (LPS) are additional receptor targets on cells or tissue.

[0108] The attachment of any positively charged ligand, such as polyethyleneimine or polylysine, to any particle may improve bioadhesion due to the electrostatic attraction of the cationic groups coating the beads to the net negative charge of the mucus. The mucopolysaccharides and mucoproteins of the mucin layer, especially the sialic acid residues, are responsible for the negative charge coating. Polyclonal antibodies raised against components of mucin or else intact mucin, when covalently coupled to particles, provide for increased bioadhesion. Similarly, antibodies directed against specific cell surface receptors exposed on the luminal surface of the intestinal tract would increase the residence time of beads, when coupled to particles using the appropriate chemistry. The ligand affinity need not be based only on electrostatic charge, but other useful physical parameters such as solubility in mucin or else specific affinity to carbohydrate groups.

[0109] Methods are known for attachment of the targeting ligands to the nanoparticles. For example, WO 2007/02493 to Semprus describes grafting sulfobetaine and carboxybetaine from self-assembled monolayers on gold substrates or from silyl groups on glass substrates using atom transfer radical polymerization (ATRP). For metallic and ceramic substrates, increased surface area can be created through surface roughening, for example by a random process such as plasma etching. Alternatively, the surface can be modified by controlled nano-patterning using photolithography. For the development of surface-functionalized gold nanoparticles as cellular probes and delivery agents, hetero-bifunctional poly(ethylene glycol) (PEG, MW 1500) having a thiol group on one terminus and a reactive functional group on the other can be synthesized for use as a flexible spacer. Using the PEG spacer, the gold nano-platform can be conjugated with a variety of biologically relevant ligands. See also El-Sayed, et al., *Nanoletters*, 5(5):829-834 (2005) describing methods for conjugating antibodies to gold nanoparticles.

[0110] D. Heat-Catalyzed Functional Agents

[0111] The nanoparticles can also be functionalized with, or administered with, one or more heat-catalyzed functional agents (HCFAs). HCFAs can be any therapeutic, prophylactic, or diagnostic agent which is bound to or associated with the shell or targeting support film of the nanoparticle, and is released (or reacted) when the particle is activated by an energy source. For example, HCFAs can be bound to the nanoparticle shell or targeting support film by a chemical bond which is cleaved as the nanoparticle is heated, releasing the HCFA. Alternatively, the HCFAs can be encapsulated in a thermally sensitive liposome or polymer microcapsule, and released upon initiation of thermotherapy at the specific site where the nanoparticles have been targeted or delivered. In some embodiments, the HCFA is an anti-neoplastic agent. In such cases, the anti-neoplastic agent is released or reacted

when and where the particle is activated by an energy source. Accordingly, the anti-neoplastic agent can be selectively administered in the vicinity of cancer cells. Administration of the anti-neoplastic agent locally and in combination with thermotherapy lowers the effective dose of anti-neoplastic agent required to treat cancer. In some embodiments, multiple HCFAs are bound to the nanoparticle and administered concomitantly.

[0112] Examples of suitable anti-neoplastic agents include, but are not limited to alkylating agents (such as cisplatin, carboplatin, oxaliplatin, mechlorethamine, cyclophosphamide, chlorambucil, dacarbazine, lomustine, carmustine, procarbazine, chlorambucil and ifosfamide), antimetabolites (such as fluorouracil (5-FU), gemcitabine, methotrexate, cytosine arabinoside, fludarabine, and floxuridine), antimicrototics (including taxanes such as paclitaxel and docetaxel and vinca alkaloids such as vincristine, vinblastine, vinorelbine, and vindesine), anthracyclines (including doxorubicin, daunorubicin, valrubicin, idarubicin, and epirubicin, as well as actinomycins such as actinomycin D), cytotoxic antibiotics (including mitomycin, plicamycin, and bleomycin), and topoisomerase inhibitors (including camptothecins such as irinotecan and topotecan and derivatives of epipodophylotoxins such as amsacrine, etoposide, etoposide phosphate, and teniposide).

[0113] Cancer immunotherapy can be effective in the treatment of select cancer patients with disease poorly amenable to conventional therapy. In preferred embodiments, the HCFA is an immunomodulator. In some embodiments, the HCFA is monoclonal antibody, for example, an epidermal growth factor receptor (EGFR) inhibitor (for example, Erbitux) or an angiogenesis inhibitor (for example, Bevacizumab). In further embodiments, the HCFA is a cytokine. Cytokines are cell-signaling proteins that are important in enhancing both innate (e.g., inflammation, macrophages) and adaptive (B- and T-cell) immune responses. Cytokines can be therapeutically administered to strengthen immune response and overcome tumor suppressive mechanisms. However, there are significant limitations to administering cytokines via traditional methods, foremost being their toxicity and poor drug half-life in circulation. Cytokines (including interferon-alpha (INF- α), interferon-beta (INF- β), interferon-gamma (INF- γ), interleukin-2 (IL-2), interleukin-12 (IL-12), and granulocyte-macrophage colony-stimulating factor (GM-CSF) can be incorporated as HCFAs and released locally when and where the particle is activated by an energy source. Accordingly, the toxicity associated with the systemic administration of cytokines can be mitigated.

III. METHOD OF TREATMENT

[0114] A. Diseases and Disorders to be Treated

[0115] The nanoparticles can be administered to an individual to kill endogenous tissue or cells. The tissue can be undesirable tissue that has arisen due to transformation, such as a tumor, cancer, or endometriosis; adipose tissue; plaques present in vascular tissue and over-proliferation such as those formed in restenosis; birthmarks and other vascular lesions of the skin; scars and adhesions; and irregularities in connective tissue or bone, such as bone spurs. As used herein, the term “cancer” includes a wide variety of malignant solid neoplasms. These may be caused by viral infection, naturally occurring transformation, or exposure to environmental agents. Parasitic infections and infections with organisms, especially fungal, that lead to disease may also be targeted.

[0116] The nanoparticles are used to diagnose or treat diseases by inducing hyperthermia in or near targeted entities. Targeted entities may include organs, cells, clusters of cells, molecules within cells or other molecular species. The diseases of interest include those where an increase in temperature of the target species brings about a desired result, and where a modest amount of localized heat may catalyze beneficial reactions, whereas a large amount of heat may be intentionally destructive. For example, heat that is sufficient and selective enough to bring about death of a targeted a cancer cell, and result in overall improvement of the patient, is preferred.

[0117] B. Pharmaceutical Formulation

[0118] Preferably, the nanoparticles are combined with one or more pharmaceutically acceptable excipients to form a pharmaceutical formulation suitable for administration to an animal or human in need thereof. Representative excipients include solvents, diluents, pH modifying agents, preservatives, antioxidants, suspending agents, wetting agents, viscosity modifiers, tonicity agents, stabilizing agents, and combinations thereof. Suitable pharmaceutically acceptable excipients are preferably selected from materials which are generally recognized as safe (GRAS), and may be administered to an individual without causing undesirable biological side effects or unwanted interactions.

[0119] The nanoparticles can be formulated for a variety of routes of administration and/or applications. In preferred embodiments, nanoparticles are administered by intravenous injection, although, depending on the application, the nanoparticles may also be administered into and/or around the target tissue, such as a tumor.

[0120] Suitable dosage forms for parenteral administration include solutions, suspensions, and emulsions. Typically, nanoparticles will be suspended in the form of a sterile aqueous solution. Acceptable solvents include, for example, water, Ringer's solution, phosphate buffered saline (PBS), and isotonic sodium chloride solution. The formulation may also be a sterile solution, suspension, or emulsion in a non-toxic, parenterally acceptable diluent or solvent such as 1,3-butanediol.

[0121] In some instances, the formulation is distributed or packaged in a liquid form. Alternatively, formulations containing nanoparticles can be packed as a solid, obtained, for example by lyophilization of a suitable liquid formulation. The solid can be reconstituted with an appropriate carrier or diluent prior to administration.

[0122] In some embodiments, the formulation is buffered with an effective amount of buffer necessary to maintain a pH suitable for administration. Suitable buffers are well known by those skilled in the art, and include acetate, borate, carbonate, citrate, and phosphate buffers.

[0123] In some embodiments, the formulation contains one or more tonicity agents to adjust the isotonic range of the formulation. Suitable tonicity agents are well known in the art and some examples include glycerin, mannitol, sorbitol, sodium chloride, and other electrolytes.

[0124] In some embodiments, the formulation contains one or more preservatives to prevent bacterial contamination. Suitable preservatives are known in the art, and include polyhexamethylenebiguanidine (PHMB), benzalkonium chloride (BAK), stabilized oxychloro complexes (otherwise known as Purite®), phenylmercuric acetate, chlorobutanol, sorbic acid, chlorhexidine, benzyl alcohol, parabens, thimerosal, and mixtures thereof.

[0125] 1. Additional Active Agents

[0126] Pharmaceutical compositions can also include one or more additional active agents. In some embodiments, the one or more additional active agents are HCFAs. In other embodiments, the one or more additional active agents do not require the addition of heat to perform a therapeutic, prophylactic, or diagnostic function when administered to a patient.

[0127] In some cases, the formulation also includes one or more small molecule anti-neoplastic agents, including any of those agents described above in Section II.D.

[0128] In some cases, the formulation also includes one or more anti-angiogenesis agents known in the art.

[0129] In cases where it is desirable to render aberrantly proliferative cells quiescent in conjunction with the administration of one or more anti-neoplastic agents, hormones and steroids (including synthetic analogs) can also be included in the formulation.

[0130] In some embodiments, one or more diagnostic agents are present in the formulation. In these embodiments, the diagnostic agent can be selected in view of the methods used to monitor treatment. Exemplary diagnostic agents include paramagnetic molecules, fluorescent compounds, magnetic molecules, and radionuclides, X-ray imaging agents, and contrast agents. In certain embodiments, such as when a PET scan is used to monitor treatment, the formulation contains a glucose analog labeled with a positron-emitting isotope such as F-18. In certain embodiments, the formulation includes 2-Deoxy-2-[¹⁸F]fluoroglucose, also known as Fluorodeoxyglucose (¹⁸F) (10E-FDG or FDG).

[0131] B. Therapy

[0132] Therapeutic methods involving the core-shell nanoparticles described above are summarized in FIG. 5. The nanoparticles (2) contain at least a core material (3) and a shell material (4). The first step (5) involves positioning the nanoparticle(s) into the region of the targeted material (1), which may be, for example, a tissue or cell. In the case of nanoparticles designed to absorb external radiation, the next step (6) is exposing the targeted region to a source of external ionizing radiation, such as an X-ray, which the core, containing one or more core-exciting, energy absorbing materials, absorbs. In the case of nanoparticles containing one or more radionuclides, this step is not required. In these embodiments, the nanoparticle core contains one or more radionuclides which decay, emitting particles that are absorbed by one or more scintillator materials located within the nanoparticle. The next step (7) involves energy transfer from the nanoparticle core material (either the core-exciting, energy absorbing materials or the scintillators) to the nanoparticle shell for the purpose of heating the shell, through any of several mechanisms, one being overlap of the core emission spectrum with the shell absorption spectra (fluorescence resonance energy transfer, FRET). As the shell is heated, it gives off heat (8). The heat (8) is transferred from the nanoparticle shell to the surrounding fluid region, which includes the targeted material or cell, to bring about the desired change, damage or cell death (9). Optionally, in a further step not illustrated in FIG. 5, the nanoparticles may be removed from the targeted material. For example, in the case of nanoparticles administered to a patient, the nanoparticle may be removed from the patient through magnetic separation from the blood, whereby blood is taken from one arm of the patient, filtered, then returned through the other arm, in a procedure similar in clinical practice to conventional kidney dialysis.

[0133] 1. Administration

[0134] The nanoparticles can be administered systemically or locally, by injection into the bloodstream, the tissue to be killed, or other lumens or cavities or vessels into the tissue or region of cells to be killed. The nanoparticles may be administered by direct injection through a syringe or catheter, preferably before the X-ray radiation is applied in the case of nanoparticles designed to absorb external core-exciting energy. In certain embodiments, the nanoparticles are directly administered to a tumor, tissue surrounding a tumor, or combinations thereof prior to or after resection.

[0135] In other scenarios, the nanoparticles are intravenously administered, thereby employing targeting schemes that depend on chemical interaction, nanoparticle size (e.g., based upon the enhanced permeability and retention (EPR) effect), or combinations thereof. Subsequently, either specific organs, parts of organs, or regions of the body are treated with the necessary dose of core-exciting energy (such as X-ray radiation), in the case of nanoparticles designed to absorb external core-exciting energy.

[0136] 2. Nanoparticle Excitation

[0137] In the case of nanoparticles containing a core-exciting energy source, such as a radionuclide, within the nanoparticle, external core-exciting energy does not have to be applied. In these cases, the appropriate amount of core-exciting energy can be controlled by selection of the appropriate isotope, as well as the amount of isotope incorporated in the nanoparticles.

[0138] In the case of nanoparticles designed to absorb core-exciting energy from an external energy source, core-exciting energy is applied following nanoparticle administration. Preferably, the core-exciting energy is applied to the particles more than 12 hours following nanoparticle administration, more preferably more than 24 hours following nanoparticle administration, so as to allow the nanoparticles (if targeted) to localize in the vicinity of the target cells or tissues.

[0139] For a given treatment session or diagnostic test, the irradiation regime to which the nanoparticles are exposed is dependent upon several factors. The compositions and design of the nanoparticle core and shell determine the amount of heat that can be emitted from the nanoparticle. Another consideration is the ability of the targeting method to deliver nanoparticles into the desired region of the cell or tissue. Another consideration is whether the objective of the procedure is diagnostic or therapeutic. Another consideration, in the case of a therapeutic method, is the maximum safe dose of radiation that can be tolerated by the patient. Another consideration, which depends upon the targeted cell or material, is the amount of heat required to bring about the desired effect.

[0140] As used herein the term “dose” represents a concentration of absorbed energy, such as electron volt (eV) per gram (gm) or Grey (Gy). The quantity termed “dose length product,” DLP, represents total energy imparted to the body and is the product of the dose and the volume of tissue exposed.

[0141] Research over the last decade involving in vivo heating of human cancers using gold nanoparticles, allows one skilled in the art to estimate the necessary energy input into gold nanoshell plasmon modes, to destroy significantly sized tumors of human cancers or other tissues. Tumors in nude mice can be killed when lasers in the 808-820 nm (NIR) wavelength range are used to irradiate skin covering a tumor of volume of less than 1 cubic centimeter (cm), for durations

ranging from 2 to 5 minutes, with surface power densities ranging from 2 to 4 Watts/cm². These literature studies are summarized in Table 3.

TABLE 3

Select Studies of NIR Heating of Gold Nanoparticles in Tumors in Mice					
Cancer Type	Type of Particle		NIR (λ , nm)	Exposure time, energy	Lit. Reference
Mice	mda-mb-435	nanorods	810 nm	5 min, 2 W/cm ²	von Maltzahn 09
Mice	ct26.wt	peg-ns 130 nm	808 nm	3 min, 4 W/cm ²	O'neal et al. '04
Mice	canine tvt	tuned-ns	820 nm	<6 min, 4 W/cm ² , 5 mm	Hirsch et al '03

[0142] Nanoparticles embedded throughout the tumor volume are responsible for the conversion of NIR into heat which causes cell death, as either NIR exposure or nanoparticle presence alone are shown to not be cytotoxic. In these studies, total laser energy deposited into the tumor is on the order of 2000 MeV. Additionally, tumors of this size are composed of, at least, billions of cancerous cells. Therefore, on a per cancer cell basis, rough estimates of 1 eV delivered into the gold shell plasmon resonance is sufficient to generate the heat necessary to bring about cancer cell death in these studies.

[0143] As a reference point for the therapeutic dosages of X-ray radiation needed, a patient of 180 cm in height and 80 Kg in weight, undergoing a state-of-the-art commercial CT scan of the chest, abdomen and pelvis (a body region approximately representing half his weight and height) may typically receive X-ray pulses with a range of energies usually 20 to 120 KeV, with an 80 KeV peak, with a total CT radiation dose (dose length product, DLP) of 1300 mGy-cm. The entire scan may represent 200 to 300 individual X-rays, separate “slices” through the examined region at a spacing of approximately two images per cm (typically about 1010 photons per cm²). State-of-the-art CT scanners submit the patient to a “cork screw” of continuous radiation, as the X-ray source rotates around the patient, from which the “slices” or images are computed. Therefore, the exposed region of the body (40 Kg and 90 cm) has received a dose of approximately 10⁸ MeV/gm. If the patient has a tumor volume of 1 cm³, of approximate density of about 1 g/cm³, that volume has received approximately 10⁸ MeV/gm of X-ray radiation. The biological response to the radiation is not considered in the DLP calculation.

[0144] In comparison to the approximate 2000 MeV of laser energy deposited into the gold plasmons, which was converted into heat to destroy nearby tumors, in the mice studies of Table 1, conventional X-ray treatments supply an ample source of energy within the body to bring about the death of cancer cells, if the energy is converted to thermal energy and targeted properly. The nanoparticles described herein are characterized by the efficient conversion of ionizing (primarily X-ray) radiation into focused thermal energy. The efficacy of treatment can be monitored in real-time, for example, if a CT-scan is used to provide the core-exciting energy. In certain embodiments, the nanoparticles are co-administered with a glucose analog labeled with a positron-emitting isotope such as F-18 (e.g., FDG). In these embodi-

ments, a PET scan can be used to monitor therapeutic efficacy in real-time, and adjust treatment parameters as required.

[0145] 3. Nanoparticle Removal

[0146] Most of the elements used in the particles are safe to administer and leave in patients. Colloidal gold particles (aurothiomalate, auranofin) have been used in the treatment of patients with rheumatoid arthritis (Jessop et al., *Br J Rheumatol* 37:992-1002, 1998; Bassett et al., *Liver Int* 23:89-9, 2003). Nanoparticle-based contrast agents for MRI, CT and PET imaging have drawn much interest. The rare-earth element gadolinium (metal chelate ion Gd^{3+}) is used in one such contrast agent, indicating the relative utility and safety of this material.

[0147] However, if desired, the nanoparticles may be designed to be removed from the patients following treatment. For example, in the case of nanoparticles administered to a patient, the nanoparticle may be removed from the patient through magnetic separation from the blood, whereby blood is taken from one arm of the patient, filtered, then returned through the other arm, in a procedure similar in clinical practice to conventional kidney dialysis.

[0148] In these embodiments, the nanoparticle core or shell material, or portion thereof, may be removed from the body. In such cases, the nanoparticle may be decorated or doped with magnetic material, typically on the shell surface, to allow magnetic removal of the particle from the blood by established cell-separation techniques.

[0149] The present invention will be further understood by reference to the following non-limiting hypothetical examples.

EXAMPLES

Example 1

Targeting Breast Cancer

[0150] The following CENT treatment approach is based on a core-shell nanoparticle designed on the basis of X-ray excited persistent luminescence and the maximum safe dose of X-ray radiation the patient may tolerate. As a reference point for the therapeutic dosages of X-ray radiation needed, the patient is 180 cm in height and 80 Kg in weight.

[0151] First, nanoparticles of $SrAl_2O_4:Eu:Dy$ of approximately 60 nm in diameter, prepared by solid state reaction methods, are used as the core in a core-shell nanoparticle material design. The X-ray luminescence spectrum of this material has a maximum at approximately 510 nm, similar to the non-doped $SrAl_2O_4$ material, as shown in FIG. 7. A nanoshell of gold is grown over the nanocore material. Gold nanoparticles have the absorbance spectrum typical of that shown in FIGS. 3 and 4; additional Mie theory calculations allow design for maximum spectral overlap (FRET) between core and shell. The nanoparticle is then coated with polyethylene glycol (PEG), to which the trastuzumab antibody is attached. The nanomaterial is further processed for preparation of intravenous administration into a patient with early stage breast cancer.

[0152] After administration of the nanoparticles, sufficient to allow targeting to the diseased cells, the patient is prepared for a CT (X-ray) irradiation regime. The therapeutic portion of the CT irradiation scheme is optimized based on several factors, including 1) the nanoparticle being used, 2) the organ or body region being treated (here, the breast), 3) the disease being treated (here breast cancer), 4) the goal of the treatment

and 5) the size of the patient (patient safety). If several exposures of X-ray radiation are to be necessary to generate the required therapeutic heating, the maximum safe dose to the patient determines the appropriate regimen.

Example 2

Treatment of Colon Cancer

[0153] The following CENT treatment approach is based on a core-shell nanoparticle designed on the basis of X-ray excited persistent luminescence and the maximum safe dose of computed tomography (CT) radiation the patient may tolerate. As a reference point for the therapeutic dosages of X-ray radiation needed, the patient is 180 cm in height and 80 Kg in weight.

[0154] First, nanoparticles of $BaFBr:Eu^{2+}, Mn^{2+}$ of 20 nm in diameter are prepared as the core material as outlined in Chen and Zhang, *J. Nanoscience and Nanotechnology* 6, 1159-1166, 2006. The X-ray luminescence spectrum of this material has a maximum at approximately 400 nm, as shown in FIG. 6A. A nanoshell of silver then is grown over the nanocore material. Silver nanoparticles have the absorbance spectrum typical of that shown in FIG. 4; additional Mie theory calculations allow design for maximum spectral overlap (FRET) between core and shell. The nanoparticle is then coated with polyethylene glycol (PEG), to which the A33 antibody is attached. The nanomaterial is further processed for intravenous administration into a patient with colorectal adenocarcinoma and/or inoperable liver metastases.

[0155] After administration of the nanoparticles, sufficient to allow targeting to the diseased cells, the patient is prepared for a PET-CT X-ray scan. PET is used initially and at the completion of treatment to identify active cancer cells (or lack thereof). The CT irradiation scheme is optimized based on several factors, including 1) the nanoparticles being used, 2) the organ or body region being treated (here, the liver), 3) the disease being treated (here colon cancer) and 4) the size and physical condition of the patient and extent of disease. Large numbers of cancer cells (for example, either large tumors or many tumors in the liver), if killed rapidly, may overload the body's ability to eliminate dead tissue, creating toxic health-threatening conditions. In such cases, the overall CENT treatment plan, and the accompanying specific irradiation regime, must be optimized for the patient, requiring a series of treatments of lower dosage CENT particles and less intense (and more regionally limited in the body) ionizing radiation.

[0156] In a related example, one inoperable but small tumor (sphere less than 1 cm in diameter), may not require a patient optimized treatment protocol; if the tumor is heat-responsive, only the irradiation protocol of a conventional CT scan of the liver (~1010 80 KeV—photons per cm^2) and a dose of CENT particles sufficient for such tumor size, may constitute the first CT treatment. Regionally-focused diagnostic PET scans, before and after treatment, determine the efficacy of the first CENT-CT treatment. If several exposures of X-ray radiation are to be necessary to generate the required therapeutic heating, the maximum safe dose to the patient determines the appropriate regimen.

[0157] In the case of extensive metastatic liver disease and a weakened patient (for example, having abnormal function of liver or kidney), the patient may undergo a set of calibration treatments to determine the optimized therapeutic treatment. The first calibration treatment involves only a limited dose of CENT-particles and radiation to kill the tumor mass that

medical experts believe the weakened patient may safely tolerate, even though active tumor will still remain. The frequency and optimization of all aspects of additional treatment are patient-dependent in such cases.

[0158] Cancer cells from a tumor biopsy may be subjected to in vitro testing to determine both the likely response to a CENT treatment and help the design and optimization of the irradiation regime for efficacy in the specific patient. Ther-motherapy may be considered either as the primary treatment or as an adjuvant therapy in combination with surgery, chemotherapy or radiation.

Example 3

Treatment of Colon Cancer Using Nanoparticles Containing a Radionuclide in the Nanoparticle Core

[0159] The following CENT treatment approach is based on a core-shell nanoparticle designed to a typical geometry of a 100-nm diameter core of Pd-103 and a 20-nm thick encasing layer of $\text{LaPO}_4\cdot\text{Ce}$, Tb and a 20-nm thick shell of gold. The radionuclide Pd-103 is an Auger electron emitter, with a 17-day half-life, that excites the Ce- and Tb-doped LaPO_4 encasing layer to emit 543-nm green light, with a quantum yield of approximately 80%. The green light is absorbed by the gold shell (See FIG. 3) and heats the nanoparticle region that contains the targeted elements of the treatment, which are colon cancer cells in blood, lymph and tissue (tumors). The maximum dose of these nanoparticles that can be safely infused is administered to the patient. As a reference point for the therapeutic dosages, the patient is 180 cm in height and 80 Kg in weight.

[0160] First, nanoparticles of Pd-103 of 100-nm in diameter are prepared as the center region of the core, by a synthesis method as outlined in *Langmuir*, 25, 7116-7128 (2009). Including chloride salts of Ce and Tb, an encasing layer of LaPO_4 is added through the methods outlined in *J. Am. Ceram. Soc.* 84:2783-92 (2001) and *Chem. Mater.* 18:4442-4446 (2006). Using standard techniques, a shell of gold is then grown over the doped lanthanum phosphate (LAP) core and coated with polyethylene glycol (PEG), to which the A33 antibody is attached using standard techniques. The nanoparticle is further processed for intravenous administration into a patient with colorectal adenocarcinoma and two inoperable liver metastases both of approximately 1 cm^3 which represents about 1 billion cancer cells. The typical colorectal cancer cell has approximately 100,000 binding sites to which the A33 antibody will bind when the A33 concentration in the blood exceeds 20 nanomolar (nM).

[0161] After administration of the nanoparticles, sufficient time (one week) is allowed for targeting to the diseased cells and treatment. Then the patient undergoes a diagnostic scan, from a MRI, CT or PET-CT device, which are used to identify active cancer cells or tumor growth. If the patient shows evidence of remaining active disease, and no significant side effects of treatment, the patient is treated again. Once the treatment protocol has ended, the patient undergoes removal of the metal-shell nanoparticles from the blood through dialysis-type technique based on magnetic separation.

1. Nanoparticles comprising:

- a) a core comprising one or more core-exciting energy absorbing materials which i) absorbs core-exciting energy, and ii) subsequently reemits energy, and

- b) a shell surrounding the core, which comprises one or more materials which absorbs the energy reemitted from the one or more core-exciting energy absorbing materials, and then emits heat in sufficient quantity to kill or damage cells or tissue.

2. The nanoparticles of claim 1, wherein the nanoparticles are nanospheres or nanorods with an average length or average diameter less than 1000 nm, preferably less than 500 nm, and most preferably less than 300 nm.

3. The nanoparticles of claim 1, wherein the one or more core-exciting energy absorbing materials are scintillators, long-lived phosphors, persistent luminescent materials, or combinations thereof.

4. The nanoparticles of claim 1, wherein the one or more core-exciting, energy absorbing materials are selected from the group consisting of

forms of strontium aluminate, such as $\text{Sr}_a\text{Al}_b\text{O}_c$, where a, b and c are integers that may vary, including $\text{Sr}_4\text{Al}_{14}\text{O}_{25}$, SrAl_2O_4 , SrAl_2O_7 , and $\text{Sr}_3\text{Al}_2\text{O}_6$;

forms of strontium aluminate doped with a rare earth element (RaE), $\text{Sr}_a\text{Al}_b\text{O}_c\text{:RaE}$, wherein a, b and c are integers that may vary and RaE=La, Lu, Ce, Pr, Nd, Sm, Eu, Tb, Dy, Ho, Er, Tm, or Yb in one or more oxidation states, including Europium(II)-doped $\text{Sr}_4\text{Al}_{14}\text{O}_{25}$, SrAl_2O_4 , SrAl_2O_7 , and $\text{Sr}_3\text{Al}_2\text{O}_6$; Dysprosium(III)-doped $\text{Sr}_4\text{Al}_{14}\text{O}_{25}$, SrAl_2O_4 , SrAl_2O_7 , and $\text{Sr}_3\text{Al}_2\text{O}_6$; and Neodymium(III)-doped $\text{Sr}_4\text{Al}_{14}\text{O}_{25}$, SrAl_2O_4 , SrAl_2O_7 , and $\text{Sr}_3\text{Al}_2\text{O}_6$;

forms of strontium aluminate co-doped with two or more different rare earth elements (RaEs), $\text{Sr}_a\text{Al}_b\text{O}_c\text{:RaE}_2$, wherein a, b and c are integers that may vary and RaE=La, Lu, Ce, Pr, Nd, Sm, Eu, Tb, Dy, Ho, Er, Tm, or Yb in one or more oxidation states, including strontium aluminate co-doped with Europium(II) and Dysprosium(III) as in $\text{Sr}_4\text{Al}_{14}\text{O}_{25}\text{:Eu}^{2+}\text{:Dy}^{3+}$, $\text{SrAl}_2\text{O}_4\text{:Eu}^{2+}\text{:Dy}^{3+}$, $\text{SrAl}_2\text{O}_7\text{:Eu}^{2+}\text{:Dy}^{3+}$, and $\text{Sr}_3\text{Al}_2\text{O}_6\text{:Eu}^{2+}\text{:Dy}^{3+}$; and strontium aluminate co-doped with Europium(II) and Neodymium(III) as in $\text{Sr}_4\text{Al}_{14}\text{O}_{25}\text{:Eu}^{2+}\text{:Nd}^{3+}$, $\text{SrAl}_2\text{O}_4\text{:Eu}^{2+}\text{:Nd}^{3+}$, $\text{SrAl}_2\text{O}_7\text{:Eu}^{2+}\text{:Nd}^{3+}$, and $\text{Sr}_3\text{Al}_2\text{O}_6\text{:Eu}^{2+}\text{:Nd}^{3+}$;

forms of rare-earth ion-doped gadolinium oxide or oxysulfide phosphor, $\text{Gd}_2\text{O}_3\text{:RaE}^{3+}$ or $\text{Gd}_2\text{O}_2\text{S:RaE}^{3+}$, wherein RaE=La, Lu, Ce, Pr, Nd, Sm, Eu, Tb, Dy, Ho, Er, Tm, or Yb;

rare-earth (RaE) ion co-doped alkaline earth aluminates, $\text{xMO+yAl}_2\text{O}_3\text{:RaE}$, RaE , where x and y are integers, and M=La, Lu, Ca, Sr, or Ba, and RaE=Ce, Pr, Nd, Sm, Eu, Tb, Dy, Ho, Er, Tm, or Yb;

rare-earth- or transition-metal-doped metal halides, including $\text{LaF}_3\text{:Ce}^{3+}$, $\text{LuF}_3\text{:Ce}^{3+}$, $\text{CaF}_2\text{:Mn}^{2+}$, $\text{CaF}_2\text{:Eu}^{2+}$, BaFBr:Eu^{2+} , BaFBr:Mn^{2+} , $\text{CaPO}_4\text{:Mn}^{2+}$, $\text{LuI}_3\text{:Ce}$, $\text{SrI}_2\text{:Eu}$, $\text{CaI}_2\text{:Eu}$, $\text{GdI}_3\text{:Ce}$; and

other suitable material including CdS, CdSe, CdTe, CaWO_4 , ZnS:Cu , TmO , ZnSe:Te , ZnS , ZnO , TiO_2 , GaN , GaAs , GaP , InAs , InP , Y_2O_3 , WO_3 , ZrO_2 , YAlO_3 :Ce, $\text{Y}_2\text{O}_3\text{:Eu}^{3+}$, $\text{CeMgAl}_{11}\text{O}_{19}\text{:Tb}$, $\text{LaPO}_4\text{:Ce}$, Tb, $\text{GdMgB}_5\text{O}_{10}\text{:Ce}$, Tb, $\text{BaMgAl}_{10}\text{O}_{17}\text{:Eu}^{2+}$, and $\text{Sr}_5(\text{PO}_4)_3\text{O:Eu}^{2+}$; and combinations thereof.

5. The nanoparticles of claim 1, wherein the core comprises a material doped with one or more rare-earth- or lanthanide-series elements of the periodic table in an amount greater than 0.05 mass percent of the total mass of the particle.

6. The nanoparticles of claim 1, wherein the one or more core-exciting, energy absorbing materials absorbs photons or

mass particles of individual energy of greater than about 1 eV, more preferably greater than about 500 eV, more preferably greater than about 30 keV.

7. The nanoparticles of claim 1, wherein the energy reemitted by the one or more core-exciting energy absorbing materials is electromagnetic radiation between about 100 nanometers and about 6000 nanometers, more preferably between about 250 nanometers and about 3000 nanometers, more preferably between 300 nanometers and 1000 nanometers.

8. The nanoparticles of claim 1, wherein the core, shell, or combinations thereof further comprise one or more radionuclides which emits core-exciting energy.

9. The nanoparticles of claim 8, wherein the one or more radionuclides have half-lives of greater than about one hour and less than about fifty years, more preferably greater than about ten hours and less than about one year, most preferably greater than about one day and less than about two months.

10. The nanoparticles of claim 8, wherein the one or more radionuclides emit one or more particle types selected from the group consisting of alpha particles, beta particles, X-rays, gamma-rays, atomic electrons, Coster-Kronig electrons, Auger electrons, and neutrons.

11. The nanoparticles of claim 8, wherein the one or more radionuclides are selected from the group consisting of Be-7, F-18, Mg-28, P-32, P-33, S-35, Ar-37, S-35, Ca-47, Sc-46, Sc-47, V-48, Cr-51, Mn-52, Mn-54, Fe-59, Fe-55, Co-58, Co-57, Co-56, Co-55, Ni-57, Cu-67, Zn-65, Ga-67, Ge-68, Se-72, Se-75, Kr-79, Rb-83, Rb-84, Rb-86, Sr-82, Sr-83, Sr-85, Sr-89, Y-88, Y-91, Zr-95, Nb-95, Tc-95m, Tc-97m, Tc-99m, Ru-97, Ru-103, Pd-103, Pd-100, Ag-111, Cd-109, Cd-115m, In-111, In-113m, In-114m, In-115m, Sn-113, Sn-117m, Sb-119, Te-118, Te-123m, I-123, I-124, I-125, I-126, I-131, Xe-122, Xe-127, Xe-131m, Xe-133, Cs-129, Cs-131, Cs-132, Ba-128, Ba-131, Ba-140, Ce-134, Ce-139, Ce-141, Pr-143, Nd-140, Pm-149, Pm-145, Sm-145, Eu-145, Eu-147, Gd-147, Gd-147, Gd-149, Gd-153, Tb-157, Dy-157, Dy-159, Er-165, Er-169, Tm-167, Tm-170, Yb-169, Ta-177, Ta-179, W-178, W-181, O-191, Ir-190, Ir-192, Pt-193, Pt-193m, Pt-195m, Au-195, Hg-197, Tl-201, Tl-202, Pb-203, and combinations thereof.

12. The nanoparticles of claim 1, wherein the shell comprises a metal selected from the group consisting of gold, silver, platinum, palladium, rhodium, ruthenium, and combinations thereof.

13. The nanoparticles of claim 1, wherein the nanoparticles further comprise one or more stabilizing materials on or within the nanoparticle core, one or more core-shell binders selected from the group consisting of phosphorus compounds and amines, and combinations thereof.

14. The nanoparticles of claim 1, wherein the nanoparticles further comprise one or more targeting molecules bound thereto.

15. The nanoparticles of claim 1, wherein the nanoparticles further comprise one or more heat-catalyzed functionalized agents bound thereto.

16. The nanoparticles of claim 1, wherein the nanoparticles comprise

a) a shell comprising a metal selected from the group that consists of gold, silver, palladium, platinum and combinations thereof;

b) a core comprising a material $\text{AlO}_3\text{:Ce}$, $\text{Y}_2\text{O}_3\text{:Eu}^{3+}$, $\text{CeMgAl}_{11}\text{O}_{19}\text{:Tb}$, $\text{LaPO}_4\text{:Ce}$, Tb , $\text{GdMgB}_5\text{O}_{10}\text{:Ce}$, Tb , $\text{BaMgAl}_{10}\text{O}_{17}\text{:Eu}^{2+}$, $\text{Sr}_4\text{Al}_{14}\text{O}_{25}\text{:Eu}^{2+}\text{:Dy}^{3+}$, $\text{SrAl}_2\text{O}_4\text{:Eu}^{2+}\text{:Dy}^{3+}$, $\text{SrAl}_2\text{O}_7\text{:Eu}^{2+}\text{:Dy}^{3+}$, and $\text{Sr}_3\text{Al}_2\text{O}_6\text{:Eu}^{2+}\text{:Dy}^{3+}$; and $\text{Sr}_5(\text{PO}_4)_3\text{Cl:Eu}^{2+}$, optionally wherein the core further comprises Pd-103; and

c) optionally a layer of polyethylene glycol bound to the surface of the nanoparticle.

17. A pharmaceutical composition comprising the nanoparticles defined by claim 1 and a pharmaceutically acceptable carrier.

18. A method for generating heat to kill or damage target cells or tissue comprising administering the nanoparticles defined by claim 1.

19. The method of claim 18, further comprising exciting the nanoparticles with an external energy source in a manner and duration such that the nanoparticles emit heat in sufficient quantity to kill, damage, affect or identify the cells or tissue to be treated.

20. The method of claim 19, wherein the external energy source is X-ray or gamma ray radiation, with an electromagnetic radiation wavelength ranging from 10.0 nm to 0.0001 nm, which may be generated from a conventional computed-tomography (CT) scanner, an X-ray or gamma-ray machine that is used in medicine, dentistry or imaging, or an X-ray laser.

21. The method of claim 20, wherein the radiation is selected from the group consisting of a pulse of radiation that is less than one second in duration, a series of radiation pulses administered over a period of time, or a continuous exposure of radiation for a period of time.

22. The method of claim 18, further comprising removing the nanoparticles from the cells or tissues following treatment.

23. The method of claim 18, wherein total energy reemitted by the one or more core-exciting energy absorbing materials during the course of treatment is at least 100 electron volts (eV) with frequencies that fall within the absorbance band of the shell material.

24. The method of claim 18, wherein the target cells or tissue are undesirable cells or tissue that has arisen due to transformation, cancerous cells or tissue, infected cells or tissue, inflamed cells or tissue, adipose cells or tissue, plaques present in vascular tissue and overproliferation, birthmarks and other vascular lesions of the skin, scars and adhesions, or irregularities in connective tissue or bone.

25. The method of claim 18, wherein the target cells or tissue are from a human, animal, or plant.

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