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- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

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(54) Title: THERAPEUTIC ELECTRON RADIATOR FOR CANCER TREATMENT

(57) Abstract: A method that produces high energy charged particles that may be used to destroy cancer cells contained in cancerous tissues. The device uses electronic neutron generators to produce neutrons with energies that have a high probability to interact with a therapeutic source comprised of a reactive material with an outer layer of a material having a high atomic number such as Platinum or Gold. The reaction produces high energy electrons, and in some cases other charged particles with relatively short half-lives, which can destroy the cancerous cells, without seriously damaging the surrounding healthy tissue.



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THERAPEUTIC ELECTRON RADIATOR FOR CANCER TREATMENT**CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims priority under 35 U.S.C. § 119(e) from: U.S. Provisional Patent Application No. 62/631,734, entitled THERAPEUTIC ELECTRON RADIATOR FOR CANCER TREATMENT, filed on February 17, 2018. The contents of the aforesaid application is incorporated herein by reference in its entirety.

BACKGROUND

1. **Field**

[0002] This invention pertains generally to the treatment of cancer and, more particularly to the treatment of highly localized carcinoma cells.

2. **Related Art**

[0003] The treatment of highly localized carcinoma cells, such as tumors, in the human body using ionizing radiation has proven to be quite effective. However, the application of ionizing radiation to the body typically involves having the radiation pass through healthy tissue before it arrives at the intended target site. This results in damage to the healthy tissue. This limits the amount of damage that can be done to the tumor at one time, resulting in the need for multiple treatments and the accumulating adverse potential biological consequences and financial costs of the treatments. If the healthy cell damage repair does not keep up with the tumor growth rate and/or metastasis rate to allow for sufficient treatment, the victim is likely to perish from the consequences of the carcinoma. Accordingly, a new method of treatment is desired that will attack the cancerous tissue with a minimal effect on the surrounding healthy tissue.

[0004] Boron Neutron Capture Therapy (BNCT) has been explored as a possible answer to the foregoing need, however, to date it has been found to lack the therapeutic range of the emitted radiation to be effective. The problem to be solved then is how to take advantage of the neutron generation and application methodology of the Boron Neutron Capture Therapy and increase the therapeutic range of the emitted radiation.

SUMMARY OF THE INVENTION

[0005] This invention overcomes the detrimental effects of the radiation treatment of cancer by providing a method of treating localized carcinoma cells in a body of an animal that includes the step of positioning a therapeutic source that is substantially nonradioactive when not exposed to a neutron source below a given activity level, but becomes a source of highly ionizing but weakly penetrating radiation, comprising high energy electrons, when exposed to a neutron field at or above the given activity level, within the body in the vicinity of the carcinoma cells. Preferably, the positioning step surgically implants the therapeutic source material on the carcinoma cells. The therapeutic source is irradiated from outside the body with a neutron field at or above the given activity level for a prescribed period of time and the irradiation step is repeated at prescribed intervals. This invention focuses on the design and operation of the therapeutic source as the irradiation target to increase the energy and range of the emitted radiation.

[0006] In one preferred embodiment the device uses electronic neutron generators to produce neutrons that interact with Boron-10 to produce Helium and Lithium ions. The B-10 material is surrounded by a very thin layer of atoms with high atomic numbers, such as Platinum or Gold. The Helium and Lithium ions are born with large kinetic energies, and when they collide with the dense electron clouds in the surrounding layers of material, large numbers of high energy Compton and photoelectrical scattered electrons are created. The emitted electrons may be used to irradiate cancerous tissue adjacent to or surrounding the emitter package. The irradiation ceases when the electronic neutron generator system is turned off. The impact of the emitted electrons is further controlled by the application of electric and/or magnetic fields positioned to accelerate the emitted electrons into a penetration depth and/or preferred irradiation direction within the patient tissue.

[0007] In another embodiment this device uses electronic neutron generators to produce neutrons with energies that have a high probability to interact with a material like Hafnium to produce prompt neutron capture gamma radiation that is used to both directly irradiate cancer cells and to produce Compton and photoelectrical electrons that irradiate cancer cells. To accomplish this, the hafnium material is surrounded by a thin layer of

atoms with high atomic numbers, such as Platinum or Gold. When Hafnium absorbs a neutron, it immediately releases a fairly high energy gamma photon. The gamma radiation primarily destroy the more radiation sensitive cancer cells within the range of the gamma photons. The resulting Hafnium isotope is generally not radioactive, so no further radiation is released unless the Hafnium daughter product then absorbs a neutron. In addition to the gamma photon damage, when the gamma radiation collides with the dense electron clouds in the surrounding layers of material, large numbers of high energy Compton and photoelectrical scattered electrons are created. The emitted electrons also irradiate cancerous tissue near to or surrounding the emitter package with a much higher probability of destroying the pernicious cells. The packages can be made in many shapes and sizes to allow them to be placed directly into or adjacent to cancerous tissue. Since the material is not radioactive unless it is being irradiated by neutrons, there is no personnel radiation exposure occurring while the material is being positioned. The irradiation ceases when the electronic neutron generator system is turned off. The impact of the emitted electrons is further controlled by the application of electric and/or magnetic fields positioned to accelerate the emitted electrons into a penetration depth and/or preferred irradiation direction within the patient tissue.

[0008] Preferably, the therapeutic source of highly ionizing, but weakly penetrating radiation is configured so it substantially only irradiates the carcinoma cells. To achieve that end a radiation shield material is formed on a side of the therapeutic source not facing the carcinoma cells. Preferably, the step of irradiating the therapeutic source includes the step of using an electric neutron generator, such as a Neutristor, to irradiate the therapeutic source. One such embodiment employs a plurality of electric neutron generators positioned around the body to irradiate the therapeutic source from different angles.

[0009] The method may also include the step of using a neutron moderating material between the electric neutron generator and the therapeutic source to adjust the neutron energy to optimize the highly ionizing, but weakly penetrating radiation produced by the therapeutic source. The neutron moderating material may be D₂O, C or other material having similar moderating properties. The neutron moderating material is placed outside the body between the electric neutron generator and the body.

[0010] In either embodiment the therapeutic source may be left within the body between treatments of treating the localized carcinoma cells, with the therapeutic source removed from the body once the treatments are complete. The therapeutic source may comprise one or more very thin disks or plates on the order of a micron thickness with a sufficient combined surface area to ensure the entire volume of localized carcinoma cells are affected by the highly ionizing but weakly penetrating radiation when one or more of the disks or plates are emplaced around the carcinoma cells and irradiated with the neutron field.

[0011] The method may also include the step of using a gamma spectrometer to monitor the intensity of gamma radiation emitted as a byproduct of the neutron radiation of the therapeutic source material and the charged particle production rate can be monitored while the neutron irradiation is occurring. The monitored intensity of the gamma radiation and neutron activity of the neutron field can be used to determine the radiation dose that has been applied to the body. The method may also control the intensity of the neutron field based on the monitored gamma intensity and the radiation dose.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] A further understanding of the invention can be gained from the following description of the preferred embodiments when read in conjunction with the accompanying drawings in which:

[0013] Figure 1 is a schematic of the apparatus that may be employed to practice the method of this invention according to one embodiment of this invention; and

[0014] Figure 2 is an illustration of a therapeutic source material according to one embodiment of this invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0015] The invention includes systems and methods for treating carcinoma cells that are localized in a body of an animal, including a subject, human, person or patient (which terms are using interchangeably herein), which include therapeutic and irradiation sources. The therapeutic source is positioned or implanted within the body of the patient and, more particularly, in the location or vicinity of the carcinoma cells. In certain

embodiments, the therapeutic source is positioned on or adjacent to the carcinoma cells. The therapeutic source includes one or more devices that include disk(s) or plate(s) or needle(s) having a thickness of about one micron. The one or more disk(s) or plate(s) or needle(s) each or together have sufficient surface area to ensure that the entire volume of the localized carcinoma cells will be affected by emitted radiation. The therapeutic source should be composed or constructed of a material that produces high energy charged particles. Suitable materials are insoluble in water and non-toxic. The neutron reaction products of the material should also be non-toxic to the patient and have very short half-lives.

[0016] The therapeutic source comprises a first material that is substantially nonradioactive without neutron irradiation at a threshold level but becomes a source of highly ionizing and weakly penetrating radiation (particles) when exposed to a neutron field above the threshold level. The threshold level may be zero or a preset intensity level. This first material is attached on at least one side to a second material. The second material has a high atomic number. Optionally, the first material is attached on two sides to a second material. The therapeutic source or the irradiation target can be configured in any number of shapes, such as needles or disks, to allow a great deal of therapeutic flexibility.

[0017] In one embodiment the first material of the irradiation target comprises Boron-10; and the second material comprises a high atomic number such as Platinum or Gold. When B-10 absorbs a thermalized neutron, it splits into highly energetic Helium and Lithium ions. A significant fraction of these nuclei collides with the electron clouds surrounding the Platinum or Gold atoms. This results in the release of many Compton and photoelectrical scattered electrons in the MeV energy range. These electrons are much more penetrating than the He and Li ions that are the basis for the current BCNT methods. Since the range of the electrons produced is still very small relative to gamma radiation treatments, the damage to healthy tissue surrounding the cancerous area is minimized. The Boron Electron Radiator Target (BERT) can be configured in a number of shapes, such as needles or disks, to allow a great deal of therapeutic flexibility.

[0018] In another embodiment the first material of the irradiation target comprises Hafnium metal; and a second material is a high atomic number such as Platinum or Gold.

When hafnium absorbs a neutron, it immediately releases gamma photons with an average energy of approximately 6 MeV. A significant fraction of these photons collides with the electron clouds surrounding the Platinum or Gold atoms. This results in the release of many Compton and photoelectrical scattered electrons in the multi-MeV energy range. Since the range of the electrons produced is still very small relative to gamma radiation treatments, the damage to healthy tissue surrounding the cancerous area is minimized. The Pulsed Neutron Capture Gamma (PNCG) Radiator Target can be configured in a number of shapes, such as needles or disks, to allow a great deal of therapeutic flexibility.

[0019] The therapeutic source material, herein interchangeably referred to as the irradiation target, is shaped using a number of commercially available fabrication techniques and, preferably, has a shielding over at least one side of the source material facing away from the carcinoma that is substantially transparent to neutrons, but shields at least some of the highly ionizing particles from the healthy tissue surrounding the carcinoma. Suitable materials include a light metal like aluminum, and like materials that have similar shielding properties. The presence of the therapeutic shield and configuration/position of the therapeutic source contributes to irradiating only the carcinoma cells, and not irradiating healthy cells.

[0020] The invention also includes an array of miniature electrically powered fast neutron generators. The neutron generators optionally have a configuration similar to the “Neutristor” design developed by Sandia National Laboratory and described in a Snowmass 2013 White Paper entitled *Novel Compact Accelerator Based Neutron and Gamma Sources for Future Detector Calibration*, G. Jennings, C. Sanzeni, D.R. Winn, Fairfield University, Fairfield CT 06824, and can be used to irradiate the therapeutic source with a neutron field once the source is implanted in the patient. Ideally, the array is configured as necessary to provide a neutron intensity at the source position sufficient to maximize the neutron reaction rate without providing too much neutron exposure to other parts of the subject’s body. Ideally, the array is geometrically configured to provide neutrons incidents on the carcinoma at different angles to provide the maximum number of sufficiently thermalized neutrons from each generator in the array to reach the target location. This can be accomplished through a combination of neutron source array

geometry and variations in the thickness of the neutron moderating material in the neutron moderator placed between the neutron array and the irradiation target. The calculations required to establish the optimum conditions can be performed by those skilled in the art using a number of different commercially available neutron transport calculation products, such as MCNP available from Los Alamos National Laboratory.

[0021] Optionally, a neutron moderator is provided that is geometrically configured, i.e., configured to mate the tissue being irradiated, includes a sufficient amount of a material like D₂O or C to be placed between each neutron generator device and the therapeutic source or irradiation target and is independently adjusted to achieve the goal of providing the maximum number of neutrons with the optimum energy for charged particle generation by neutron reactions with the therapeutic source or irradiation target.

[0022] Desirably, a gamma spectrometer is provided that measures the intensity of the gamma radiation emitted by the target isotope created in the neutron reaction so the charged particle production rate can be monitored while the neutron irradiation is occurring. This can be accomplished using a number of commercially available devices.

[0023] A computational control system uses the measured gamma activity and/or the activity status of the neutron generators to determine radiation dose that has been applied to the patient relative to a dose target. The control system has the ability to increase or decrease the intensity of the neutrons provided by any or all of the neutron generators in the array based on gamma intensity and measured dose measurements.

[0024] The dose of neutron irradiation applied can also be adjusted via neutron generator power according to the desired therapeutic effect in combination with the geometry of neutron generators and neutron moderator. Likewise, the duration of irradiation can also be adjusted.

[0025] Figure 1 shows a system for treating highly localized carcinoma cells in accordance with this invention. The system employs one or more therapeutic source material **10** (Figure 2) with sufficient surface area to ensure that the entire volume of the localized carcinoma cells will be affected by the radiation emitted when exposed to a neutron field. In one embodiment, the therapeutic source material **10** comprises very thin (e.g., micron thickness) disks or plates with sufficient surface area to ensure that the entire volume of the localized carcinoma cells will be affected by the radiation emitted

when one or more of the devices are implanted within a patient **12** proximate to, and preferably adjacent the tumor tissue **22** and irradiated with neutrons **30** from electronic neutron generators device **14**. The therapeutic source material **10** used should be one that produces high energy charged particles. The therapeutic source material **10** must be insoluble in water and non-toxic. The neutron reaction products of the therapeutic source material **10** should also be non-toxic to the subject and have very short half-lives.

[0026] Figure 1 also provides a schematic illustration of an embodiment of the design of the irradiation target **10**, also referred to as the therapeutic source material **10**. The figure shows a representation of the neutron generator device **14** comprising an array of neutron generators **32** that can be configured to provide the neutron energy and dose distribution at the site of the irradiation target **10** through a combination of distance from the patient **12** and neutron moderator **16** (typically made of a flexible moderating material), such as a configurable mass of a highly hydrogenous material or various amounts of deuterium contained in a specially configured plastic container, i.e., configured to match the contour of the tumor tissue **22** being irradiated, positioned between the neutron generator device **14** and the patient **12**.

[0027] As shown in Figure 2, the therapeutic source material **10** comprises a first material **26** that is substantially nonradioactive without neutron irradiation at a threshold level but becomes a source of highly ionizing and weakly penetrating radiation (particles) when exposed to a neutron field above the threshold level. The threshold level may be zero or a preset intensity level. The first material **26** is attached on at least one side to a second material **28**. The second material **28** has a high atomic number. Optionally, the first material **26** is attached on two sides to a second material **28** (Figure 2). The therapeutic source material **10** or the irradiation target **10** can be configured in any number of shapes, such as needles or disks, to allow a great deal of therapeutic flexibility.

[0028] In one embodiment the first material **26** of the irradiation target **10** comprises a thin layer of B₄C composed of mostly Boron-10 (1 μm) sandwiched between very thin (1 μm thick) sheets of a second material **28** with a high atomic number such as Platinum or Gold.

[0029] In another embodiment the first material **26** of the irradiation target **10** comprises a thin layer of natural Hafnium metal (1 mm) sandwiched between very thin (1 mm thick) sheets of a material **28** with a high atomic number such as Platinum or Gold.

[0030] The therapeutic source material **10**, i.e., the irradiation target **10**, to be inserted for irradiation can be shaped using a number of commercially available fabrication techniques and, preferably, has a shielding over at least one side of the source material facing away from the carcinoma that is substantially transparent to neutrons, but shields at least some of the highly ionizing particles from the healthy tissue surrounding the carcinoma. Such a shield may be constructed out of a light metal, optionally aluminum.

[0031] An array of miniature electrically powered fast neutron generators **32** can be used to irradiate the therapeutic source material **10** with a neutron field once the source material **10** is implanted in the patient. Ideally, the array is configured as necessary to provide a neutron intensity at the source position sufficient to maximize the neutron reaction rate without providing too much neutron exposure to other parts of the subject's body. Ideally, the array is geometrically configured to provide neutrons incidents on the carcinoma at different angles to provide the maximum number of sufficiently thermalized neutrons **30** from each generator in the array to reach the target location. This can be accomplished through a combination of neutron source array geometry and variations in the thickness of the neutron moderating material in the neutron moderator **16** placed between the neutron array and the irradiation target **10**.

[0032] Preferably, a neutron moderator **16** is provided that is geometrically configured, i.e., configured to mate the tissue being irradiated, includes a sufficient amount of a material like D₂O or C to be placed between each neutron generator device **14** and the therapeutic source material or irradiation target **10** and is independently adjusted to achieve the goal of providing the maximum number of neutrons **30** with the optimum energy for charged particle generation by neutron reactions with the therapeutic source material or irradiation target **10**.

[0033] A gamma spectrometer **18** is provided that measures the intensity of the gamma radiation emitted by the target isotope created in the neutron reaction so the charged particle production rate can be monitored while the neutron irradiation is occurring. This can be accomplished using a number of commercially available devices.

[0034] A computational control system **20** uses the measured gamma activity and the activity status of the neutron generators **32** to determine radiation dose that has been applied to the patient **12** relative to a dose target. The control system **20** has the ability to increase or decrease the intensity of the neutrons provided by any or all of the neutron generators **32** in the array based on gamma intensity and measured dose measurements.

[0035] The dose of neutron irradiation applied can also be adjusted via neutron generator power according to the desired therapeutic effect in combination with the geometry of neutron generators **32** and neutron moderator **16**. Likewise, the duration of irradiation can also be adjusted.

[0036] Optionally, the external electric and/or magnetic field can be manipulated through electric field plate **24** to change the kinetic energy and primary direction of movement of the electrons emitted from the irradiator target **10** to better control the applied dose to the patient. As an example, application of an oscillating electric field will allow the radiated electrons to be accelerated beyond, or suppressed from, the range dictated by the kinetic energy imparted by the gamma photon collisions with the Gold or Platinum electrons. Application of an external magnetic field could be used to concentrate the emitted electron density nearer to or further from the emitter element.

[0037] The method and system for treating carcinoma described herein is different from other types of radiation treatments in that it relies on creating and implanting a non-radioactive target in or around a tumor versus the injection of a compound that provides a limited amount of therapeutic treatment deposition in the desired area. The ability this system provides to perform neutron activation of initially non-radioactive materials in a hospital environment maximizes the benefits of charged particle cancer treatment and minimizes the unwanted expense and radiation exposure to the patient and caregivers. This approach allows very precise and efficient cancer killing to occur. Additionally, the target source can be left in position without increasing the whole body radiation dose to the patient, until the tumor is completely dead. Multiple irradiations can occur with relative ease. The use of the neutristor neutron generator provides the ability to perform the treatments in a hospital setting instead of a reactor or very large neutron source location. This greatly reduces treatment costs (or greatly increases treatment profitability) relative to existing radiation treatment methods.

[0038] While specific embodiments of the invention have been described in detail, it will be appreciated by those skilled in the art that various modifications and alternatives to those details could be developed in light of the overall teachings of the disclosure. Accordingly, the particular embodiments disclosed are meant to be illustrative only and not limiting as to the scope of the invention which is to be given the full breadth of the appended claims and any and all equivalents thereof.

What is claimed is:

1. A method of treating localized carcinoma cells (22) in a body (12) of an animal comprising the steps of:

positioning a therapeutic source (10) comprising a first material (26) having an outer layer of a second material (28) having a high atomic number, wherein the therapeutic source (10) is substantially nonradioactive when not exposed to a neutron field (30), but becomes a source of highly ionizing but weakly penetrating radiation when exposed to the neutron field (30) within the body (12) in the vicinity of the carcinoma cells (22);

irradiating the therapeutic source (10) from outside the body with a neutron field (30) at or above the given activity level for a prescribed period of time; and

repeating the irradiating step at prescribed intervals.

2. The method of treating localized carcinoma cells (22) of Claim 1 wherein the second material (28) is platinum, gold, or a combination thereof.

3. The method of treating localized carcinoma cells (22) of Claim 1 or 2 wherein the therapeutic source (10) of highly ionizing but weakly penetrating radiation is configured to substantially only irradiates the carcinoma cells (22).

4. The method of treating localized carcinoma cells (22) of any previous claim wherein a radiation shield material that shields at least some of the highly ionizing radiation, but is substantially transparent to neutrons, is formed on a side of the therapeutic source (10) not facing the carcinoma cells (22).

5. The method of treating localized carcinoma cells (22) of Claim 4 wherein the radiation shield material comprises aluminum.

6. The method of treating localized carcinoma cells (22) of any previous claim wherein the positioning step includes the step of surgically implanting the therapeutic source (10) approximately on the carcinoma cells (22).

7. The method of treating localized carcinoma cells (22) of any previous claim wherein the step of irradiating the therapeutic source (10) includes the step of using an electric neutron generator device (14) to irradiate the therapeutic source (10).

8. The method of treating localized carcinoma cells (22) of 7 wherein the electric neutron generator device (14) includes a plurality of electric neutron generators (32) positioned around the body (12) to irradiate the therapeutic source (10) from different angles.

9. The method of treating localized carcinoma cells (22) of any previous claim further comprising the step of using a neutron moderating material (16) between the electric neutron generator (32) and the therapeutic source (10) to adjust the neutron energy to optimize the highly ionizing, but weakly penetrating radiation produced by the therapeutic source (10).

10. The method of treating localized carcinoma cells (22) of Claim 9 wherein the neutron moderating material (16) comprises D₂O or C.

11. The method of treating localized carcinoma cells (22) of Claim 1 wherein the therapeutic source (10) comprises one or more very thin disks or plates on the order of a micron in thickness with a sufficient combined surface area to ensure the entire volume of localized carcinoma cells (22) is affected by the highly ionizing but weakly penetrating radiation when one or more of the disks or plates are emplaced around the carcinoma cells (22) and irradiated with the neutron field (30).

12. The method of treating localized carcinoma cells (22) of Claim 1 further comprising the step of using a gamma spectrometer (18) to monitor an intensity of gamma radiation emitted by a product of neutron radiation of the therapeutic source (10), and to monitor a charged particle production rate, while the neutron irradiation is occurring.

13. The method of treating localized carcinoma cells (22) of any previous claim wherein the first material (26) comprises primarily Boron-10.

14. The method of treating localized carcinoma cells (22) of any previous claim wherein the first material (26) comprises B₄C.

15. The method of treating localized carcinoma cells (22) of any previous claim wherein the first material (26) comprises Hafnium.

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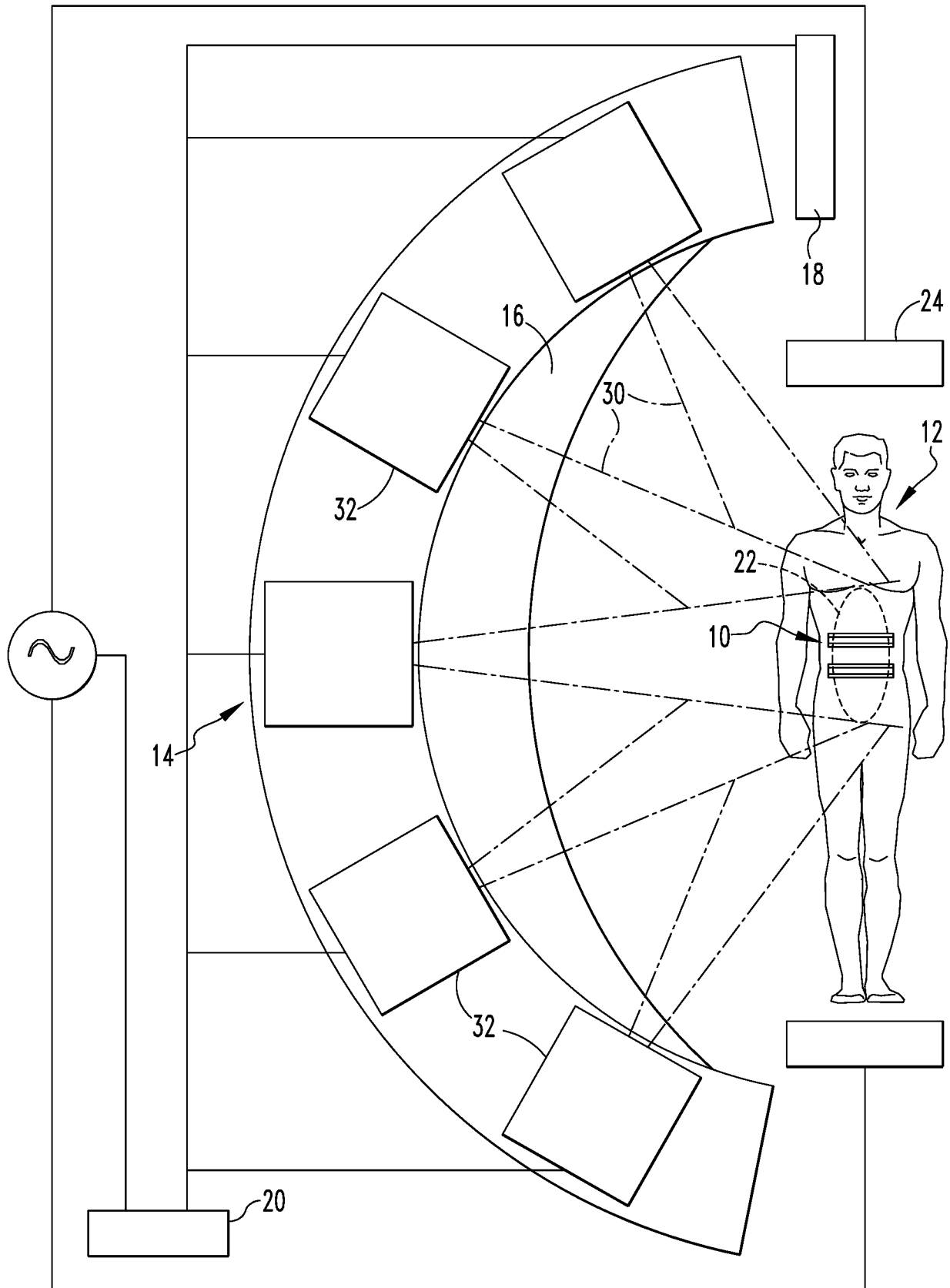
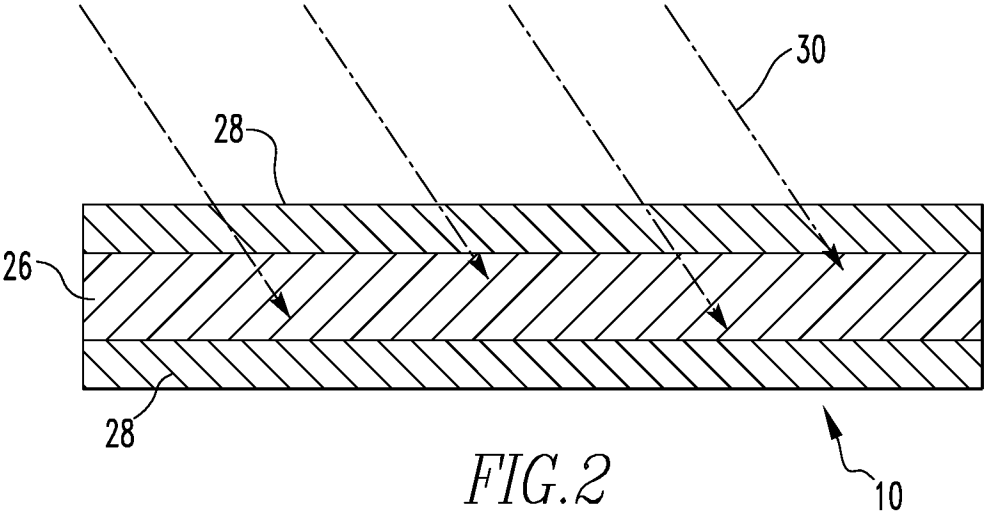


FIG. 1



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/017821**A. CLASSIFICATION OF SUBJECT MATTER****A61K 41/00(2006.01)i, A61N 5/10(2006.01)i**

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 41/00; A61N 5/00; A61P 35/00; A61N 5/10

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

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

eKOMPASS(KIPO internal) & Keywords: radiator, cancer, treatment, therapeutic electron, boron-10, platinum, gold, carcinoma, nonradioactive, neutron field**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005-107387 A2 (PROPHARMACEUTICALS, INC.) 17 November 2005 See abstract; and claims 13, 14.	1-3, 11, 12
A	WO 2015-017034 A1 (GOURDIE, R. G. et al.) 05 February 2015 See abstract; and 140, 146.	1-3, 11, 12
A	US 2004-0181114 A1 (HAINFELD, J. F. et al.) 16 September 2004 See abstract; and claims 1, 7, 8.	1-3, 11, 12
A	KASPAR, H. et al., "Gold nanoparticles for cancer radiotherapy: a review", Cancer Nano., 2017, Vol. 7, No.8, pages 1-20 See abstract.	1-3, 11, 12
A	SETUA, S. et al., "Cisplatin-tethered gold nanospheres for multimodal chemo-radiotherapy of glioblastoma", Nanoscale, 2014, Vol. 6, No. 8, pages 10865-10873 See abstract.	1-3, 11, 12



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

04 June 2019 (04.06.2019)

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Name and mailing address of the ISA/KR

International Application Division

Korean Intellectual Property Office

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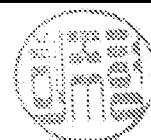


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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2019/017821

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORTInternational application No.
PCT/US2019/017821**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 5,8,10
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 5, 8, 10 are unclear since they refer to claims which are not searchable due to not being drafted in accordance with Rule 6.4(a).
3. ☒ Claims Nos.: 4,6,7,9,13-15
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.