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(54) **Title:** A COMPACT 7 MEV TO 11 MEV CYCLOTRON FOR MEDICAL ISOTOPES PRODUCTION

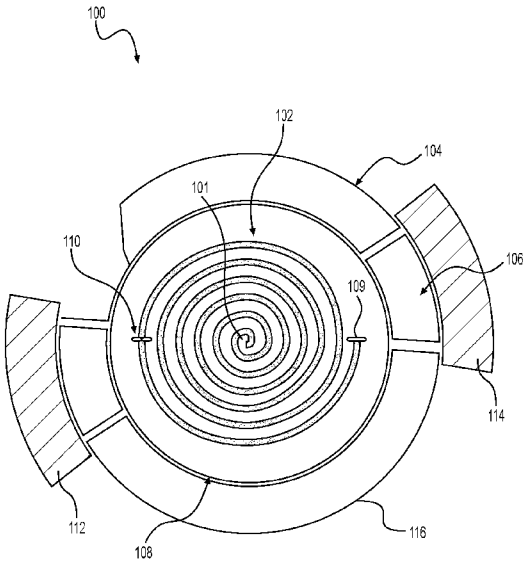

FIG. 2

(57) **Abstract:** The apparatus and methods for producing radiochemical include a cyclotron for generating a beam of charged particles having a beam envelope consisting essentially of particles having an energy in the range of 7 MeV to 11 MeV; an accelerator for directing the beam of charged particles along a path; a plurality of targets positioned within or outside of the cyclotron, the plurality of targets positioned in the path of the beam of charged particles; the targets including a target substance having a composition selected for producing a radioactive substance during interaction with the beam of charged particles; wherein the target substance is in a solid, gaseous or liquid state; a radiochemical synthesis subsystem integrated with the cyclotron, the radiochemical synthesis subsystem having one or more of microreactor or microfluidic chip, wherein the radiochemical synthesis subsystem for receiving the radioactive substance, for receiving at least one reagent to synthesize the radiochemical.

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A COMPACT 7 MEV TO 11 MEV CYCLOTRON FOR MEDICAL ISOTOPES PRODUCTION

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims priority under 35 U.S.C. §119 to U.S. Provisional Patent Application No. 63/471,954, filed on June 8, 2023, hereby incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates generally to cyclotrons and particularly to a compact, self-shielded, high energy 7 MeV to 11 MeV having a beam current up to 100 micro-Amperes cyclotron system for medical isotope and biomarker production including clinical and research applications.

BACKGROUND

[0003] Cyclotrons are used to generate high energy charged particle beams for purposes such as nuclear physics research and medical treatments. One area where cyclotrons have found particular utility is in the generation of radiopharmaceuticals, also known as biomarkers, for medical diagnosis by such techniques as positron emission tomography (PET). A conventional cyclotron involves a substantial investment, both in monetary and building resources. An example of one of the more compact conventional cyclotrons used for radiopharmaceutical production is the Eclipse RD. The self-shielded version of the Eclipse RD can be installed in a facility without a shielded vault. The minimum room size for housing the Eclipse RD is 7.31 m×7.01 m×3 m (24 ft×23 ft×10 ft). To support the approximately 29,300 kg (64,400 lbs.) installed weight of a self-shielded Eclipse RD, the cyclotron room includes a concrete pad with a

minimum thickness of 36 cm (14 in). In addition to a large size and weight, the power requirements often involve a dedicated and substantial electrical power system. The minimum electrical service required for the Eclipse RD is a 208 (±5%) VAC, 150 A, 3-phase service. Thus, medical facilities have a need for biomarkers, but the monetary, structural, and power requirements of conventional cyclotrons have historically made it impracticable for most hospitals and other medical facilities to produce biomarkers on-site.

[0004] A biomarker is used to interrogate a biological system and can be created by "tagging" or labeling certain molecules, including biomolecules, with a radioisotope. A biomarker that includes a positron-emitting radioisotope is required for positron-emission tomography (PET), a noninvasive diagnostic imaging procedure that is used to assess perfusion or metabolic, biochemical and functional activity in various organ systems of the human body. Because PET is a very sensitive biochemical imaging technology and the early precursors of disease are primarily biochemical in nature, PET can detect many diseases before anatomical changes take place and often before medical symptoms become apparent. PET is similar to other nuclear medicine technologies in which a radiopharmaceutical is injected into a patient to assess metabolic activity in one or more regions of the body. However, PET provides information not available from traditional imaging technologies, such as magnetic resonance imaging (MRI), computed tomography (CT) and ultrasonography, which image the patient's anatomy rather than physiological images. Most clinically-important positron-emitting radioisotopes are produced in a cyclotron, a radioisotope generator well known in the prior art.

[0005] Cyclotrons have been known for many years. A cyclotron is one type of particle accelerator in which charged particles are accelerated through a substantially spiral path using the forces of electrical potential and magnetic fields. The first cyclotron was invented by Ernest

O. Lawrence in 1929–1930 at the University of California, Berkeley, for which he was awarded the Nobel Prize in Physics in 1939. A cyclotron accelerates a charged particle beam using a high frequency alternating voltage which is applied between two hollow "D"-shaped sheet metal electrodes called “dees” inside a vacuum chamber. The path of the accelerated particle is then bent by a magnetic field into a spiral path (due to the Lorentz force perpendicular to their direction of motion), which tends to cause the particle to be directed back across the gap. By alternately changing the polarity of the electrodes by means of a radio-frequency generating system, the particles are accelerated with each crossing of the gap, thereby increasing the radius of the spiral path of the accelerated particles. When the accelerated particles reach the rim of the chamber a small voltage on a metal plate deflects the beam and hits a target located at the exit point at the rim of the chamber.

[0006] For example, U.S. Patent Nos. 7,476,883 and 8,080,815 to Ronald Nutt, and U.S. Patent No. 11,135,321B2 to Khachaturian et al., incorporated herein by reference in their entirety disclose prior-art biomarker generator cyclotron systems. As illustrated in FIG. 1, the prior art cyclotron described in U.S. Patent No. 7,476,883 to Ronal Nutt discloses a two-pole cyclotron **10**, which includes a magnet system having four magnet poles, each defining a wedge shape. The upper magnet poles **26**, **28** protrude downward from the upper magnet yoke **54**, toward the lower magnet poles **30**, **32** which protrude upward from the lower magnet yoke **56**. The magnetic field, which is represented by the arrows **58**, is perpendicular to the longitudinal plane of the “dees” and, therefore, is perpendicular also to the electric field generated by the alternating high voltage. The magnetic field exerts a force that is perpendicular both to the direction of motion of the charged particle and to the magnetic field. Hence, a charged particle in a magnetic field having a constant strength undergoes circular motion if the area defined by

the magnetic field is sufficiently large. The diameter of the circular path of the charged particle is dependent on the velocity of the charged particle and on the strength of the magnetic field. It is prudent to note that a magnetic field causes a charged particle to change direction continuously; however, it does not alter the velocity of a charged particle, hence the energy of the charged particle is unaffected.

[0007] The magnet poles are often called "hills," and the hills define recesses that are often called "valleys." In FIG. 1, all four of the hills **26**, **28**, **30**, **32** and two of the four valleys **34**, **36** are visible. The beam **40**, during acceleration, is exposed alternately to the strong and weak magnetic fields defined respectively by the hills and valleys along its path to the extraction radius. As the beam **40** passes through each hill region, it bends sharply due to the effect of the strong magnetic field. While in the valley regions, however, the beam trajectory is more nearly a straight path toward the next hill region. This alternating magnetic field provides strong vertical focusing forces to beam particles straying from the median plane during acceleration. These focusing forces direct straying particles back toward the median plane, promoting high beam extraction efficiencies.

[0008] As indicated previously, the RF system of a cyclotron supplies an alternating high voltage potential to the dees. As shown in the embodiment of the two-pole cyclotron depicted in FIG. 1, each of the two dees **12**, **14** is mounted in a valley region. The beam **40** of positively-charged particles gains energy by being attracted by the dee when the dee has a negative charge, and then by being repelled from the dee as the dee changes to a positive charge. Thus, because a charged particle within the beam **40** passes through both dees **12**, **14** in the course of a single orbit, that charged particle undergoes two increments of acceleration per orbit. Therefore, with every acceleration, the beam **40** of charged particles gains a known, fixed

quantity of energy, and its orbital radius increases in predetermined fixed increments until it reaches the extraction radius, which corresponds to the extraction energy of the beam. The ion source system **80** is required for generating the charged particles for acceleration. Although several ion source systems are well known in the prior art, in the interest of brevity, only one of these systems is summarized below. Those skilled in the art will acknowledge that an ion source system comprising an internally, axially-mounted Penning Ion Gauge (PIG) ion source optimized for proton (H^+) production is useful for producing Fluorine-18, among other positron-emitting radioisotopes. This ion source system ionizes hydrogen gas using a strong electric current. The ionized hydrogen gas forms plasma, from which protons (H^+ ions) are extracted for acceleration using a bias voltage.

[0009] After the beam **40** of charged particles acquires its extraction energy, it is directed into the target system **88**. Target systems are well known in the prior art and they generally operate as follows: The beam exits the magnetic field **58** at the predetermined location **90** and enters the accelerator beam tube **92**, which is aligned with the target entrance **94**. A collimator **96**, which consists of a carbon disk defining a central hole, is mounted at the target entrance **94**, and as the beam **40** passes through the collimator **96**, the collimator **96** refines the profile of the beam. The beam **40** then passes through the target window **98**, which consists of an extremely thin sheet of foil made of a high-strength, non-magnetic material such as molybdenum. Thereafter, the beam **40** encounters the target substance **100**, which is positioned behind the target window **98**. The beam **40** bombards the target substance **100**, which may comprise a gas, a liquid, or a solid, generating the desired radioisotope through a nuclear reaction.

[0010] Developments in the radionuclide production process have been observed in only some cases. More research and development are needed in cyclotron improvements to make novel radionuclide available for the medical industry. While the prior art cyclotron has been used worldwide to produce radionuclides, there is a need for a next generation compact cyclotron situated next to the positron emission tomography (PET) and computed tomography (CT) scan table to accelerate the protons at higher energies of up to 11 MeV or even 15 MeV with increased proton beam current capabilities capable of producing multiple batches of biomarkers including ^{18}FDG, Na^{18}F, ^{18}F-MISO, ^{18}FLT, ^{18}F-Choline, ^{18}F-DOPA and ^{18}F-PSMA, as well as N^{13} ammonia, C^{11} labelled compounds, Cu^{64}, as well as Ga^{68} compounds, "on demand", even in a small hospital facility or medical clinic. Further, there is a need for a versatile cyclotron to produce different radioisotopes for pre-clinical and research applications.

[0011] Thus, apparatuses and methods for producing a compact cyclotron for medical isotopes and biomarker production addressing the aforementioned needs and problems are desired.

SUMMARY OF INVENTION

[0012] Embodiments include apparatuses, systems and methods related to the use of a compact, self-shielded, proton cyclotron for producing a radiochemical. The compact, self-shielded cyclotron system for producing a radiochemical includes a cyclotron for generating a beam of charged particles having a beam envelope consisting essentially of particles having an energy in the range of 7 MeV to 11 MeV; an accelerator for directing the beam of charged particles along a path; a plurality of targets positioned within or outside of said cyclotron, said plurality of targets positioned in the path of the beam of charged particles; said targets comprising a target substance having a composition selected for producing a radioactive

substance during interaction with the beam of charged particles; wherein said target substance is in a solid, a gaseous or a liquid state; a radiochemical synthesis subsystem integrated with or in communication with said cyclotron, said radiochemical synthesis subsystem having one or more of a microreactor or a microfluidic chip, wherein said radiochemical synthesis subsystem for receiving the radioactive substance, for receiving at least one reagent to synthesize the radiochemical and for synthesizing the radiochemical.

[0013] In exemplary embodiments, the radioactive substance is a positron-emitting substance selected from the group consisting of F-18, C-11, N-13, Ga-68, O-15, Cu-64, Ga 67, In 111, I-123, Zr-89, Tc-99m, Pd-103 and Ac-225.

[0014] The compact, self-shielded cyclotron system includes a method for producing single or multiple doses of a PET biomarker. The method for producing single or multiple doses of a PET biomarker includes the steps of: (a) providing a compact cyclotron system for generating a beam of charged particles, the beam consisting essentially of protons having an energy in a range of 7 MeV to 11 MeV; (b) generating the beam of charged particles consisting essentially of a beam of protons using a particle accelerator associated with the cyclotron system; (c) bombarding one or more target substances with the beam consisting essentially of protons to produce one or more radioactive substances corresponding to one or more of the target substances; (d) providing a radiochemical synthesis subsystem having one or more of a microreactor or a microfluidic chip, said radiochemical synthesis subsystem for receiving the one or more radioactive substances, for receiving at least one reagent to synthesize the one or more radioactive substances, and for synthesizing from the one or more radioactive substances one or more unit doses of the one or more (PET) biomarkers corresponding to the one or more radioactive substances synthesized by the radiochemical synthesis subsystem; (e) transferring the

one or more radioactive substances to said radiochemical synthesis subsystem; (f) transferring the at least one reagent to said radiochemical synthesis subsystem; and (g) synthesizing the one or more unit doses of the one or more (PET) biomarkers by said radiochemical synthesis subsystem. The one or more PET biomarkers is selected from the group consisting of 18FDG, Na18F, 18F-MISO, 18FLT, 18F-Choline, 18F-DOPA and 18F-PSMA.

[0015] These and other features of the present invention will become readily apparent upon further review of the following specification and drawings.

DESCRIPTION OF THE DRAWINGS

[0016] FIG. 1 is an exploded view of a diagrammatic illustration of certain components of a prior art biomarker generator (BG) cyclotron.

[0017] FIG. 2 schematic illustrating an overview of an embodiment of the 7 MeV to 11 MeV cyclotron illustrating the proton cyclotron according to an embodiment of the present invention.

[0018] FIG. 3 is a schematic illustrating an embodiment of the 7 MeV to 11 MeV cyclotron having a beam envelope, a beam line and multiple internal and/or external targets according to an embodiment of the present invention.

[0019] FIG. 4 is a plan view of the biomarker generator (BG) cyclotron system with various components in the cyclotron room and the GMP room including a computer which controls the cyclotron and the radiopharmaceutical synthesis subsystem for producing the biomarker according to an embodiment of the present invention.

[0020] FIG. 5 is a block diagram of a biomarker generator system including the improved cyclotron described herein for producing a unit dose or multi-unit doses of a biomarker according to an embodiment of the present invention.

[0021] FIG. 6 is a flow diagram of an exemplary embodiment of a fully automated method for producing one unit dose or multi-unit doses of a biomarker using the improved and novel biomarker generator cyclotron system according to an embodiment of the present invention.

[0022] Unless otherwise indicated, similar reference characters denote corresponding features consistently throughout the attached drawings.

DETAILED DESCRIPTION

[0023] The present disclosure relates to apparatuses, systems and methods for the use of an improved, compact, self-shielded 7 MeV to 11 MeV proton cyclotron for producing radiochemicals or biomarkers for positron-emission tomography (PET)/computed tomography (CT) medical applications including research applications. An improved compact cyclotron system and a method suitable for efficiently producing short lived radiopharmaceuticals in unit dose and multi-unit doses is described in detail herein and illustrated in the accompanying figures. The improved compact cyclotron system includes a particle accelerator and a radiopharmaceutical synthesis subsystem integrated with or in communication with the cyclotron, which are controlled by a computer. The radiochemical synthesis subsystem of the improved compact cyclotron is a small volume chemical synthesis system comprising a microreactor and/or a microfluidic chip and optimized for synthesizing the radiochemical in quantities on the order of one unit dose or multi-unit doses allowing for significant reductions in the quantity of

radioisotope required and in the processing time as compared to conventional radiopharmaceutical processing systems.

[0024] Embodiments are described of the compact, self-shielded cyclotron system for producing a radiochemical, said system includes a cyclotron for generating a beam of charged particles having a beam envelope consisting essentially of particles having an energy in the range of 7 MeV to 11 MeV; an accelerator for directing the beam of charged particles along a path; a plurality of targets positioned within or outside of said cyclotron, said plurality of targets positioned in the path of the beam of charged particles; said targets comprising a target substance having a composition selected for producing a radioactive substance during interaction with the beam of charged particles; wherein said target substance is in a solid, a gaseous or a liquid state; a radiochemical synthesis subsystem integrated with or in communication with said cyclotron, said radiochemical synthesis subsystem having one or more of a microreactor or a microfluidic chip, wherein said radiochemical synthesis subsystem for receiving the radioactive substance, for receiving at least one reagent to synthesize the radiochemical and for synthesizing the radiochemical.

[0025] In an embodiment, the self-shielded compact cyclotron system for producing a radiochemical can have a beam current in the range of about 1 to about 100 micro-Amperes. The target includes a plurality of liquid internal targets positioned within the cyclotron or an external solid or gaseous target positioned external to the cyclotron. The compact cyclotron system can further include a beam collimator to direct the beam of charged particles to a solid or a gaseous target positioned external to or outside the cyclotron. The beam of charged particles consists essentially of protons having an energy of approximately 9 MeV to 11 MeV. The cyclotron system further includes a shield positioned externally to surround the cyclotron to reduce a

radiation field generating from the beam of charged particles to an acceptable level, such as of less than 1 millirem/hr. Additionally, in some instances, the cyclotron can be modified to produce energies greater than 11 MeV up to 15 MeV. Such modifications will readily be apparent to those skilled in the art, using the guidance of the instant disclosure.

[0026] In an embodiment, the compact self-shielded cyclotron system for producing a radiochemical further includes a computer controller system configured in communication with the cyclotron and the radiochemical synthesis subsystem to control the cyclotron to generate and deliver the beam of charged particles for irradiation of the target and to control the radiochemical synthesis subsystem. The computer controller can move and position the target in the path of the beam of charged particles. The computer controller system can include a user interface to enable selection of a radiopharmaceutical for radiochemical synthesis by the radiochemical synthesis subsystem, wherein the selection can be for the production of FDG-F18 or NH2-N13 radiochemical, for example.

[0027] In an embodiment, the compact, self-shielded cyclotron system for producing a radiochemical includes a permanent magnet for directing the beam as the beam is being accelerated by the accelerator. The radioactive substance includes a radioisotope that emits positrons, which includes a (PET) biomarker. In an embodiment, the (PET) biomarker can be selected from the group consisting of F-18, C-11, N-13, Ga-68, O-15, Cu-64, Ga 67, In 111, I-123, Zr-89, Tc-99m, Pd-103 and Ac-225, for example. The radiochemical is substantially radio-chemically pure that is ready to provide a radiochemical that is ready for use in patients and *in-vitro* and *in-vivo* applications.

[0028] In another embodiment, the method for producing single or multiple doses of one or more (PET) biomarkers includes the steps of: (a) providing a compact cyclotron system for generating a beam of charged particles, the beam consisting essentially of protons having a minimum energy between 7 MeV to 11 MeV; (b) generating the beam of charged particles consisting essentially of a beam of protons using a particle accelerator associated with the cyclotron system; (c) bombarding one or more target substances with the beam consisting essentially of protons to produce one or more radioactive substances corresponding to one or more of the target substances; (d) providing a radiochemical synthesis subsystem having one or more of a microreactor or a microfluidic chip, said radiochemical synthesis subsystem for receiving the one or more radioactive substances, for receiving at least one reagent to synthesize the one or more radioactive substances, and for synthesizing from the one or more radioactive substances one or more unit doses of the one or more (PET) biomarkers corresponding to the one or more radioactive substances synthesized by the radiochemical synthesis subsystem; (e) transferring the one or more radioactive substances to said radiochemical synthesis subsystem; (f) transferring the at least one reagent to said radiochemical synthesis subsystem; and (g) synthesizing the one or more unit doses of the one or more (PET) biomarkers by said radiochemical synthesis subsystem. The method for the producing single or multiple doses of a (PET) biomarker desirably is fully automated.

[0029] In an embodiment of the method for producing single or multiple doses of one or more (PET) biomarkers, a computer controller controls the synthesis of one or more unit doses of the one or more (PET) biomarkers. The radioactive substance is a positron-emitting substance selected from the group consisting of F-18, C-11, N-13, Ga-68, O-15, Cu-64, Ga 67, In-111, I-123, Zr-89, Tc-99m, Pd-103 and Ac-225, for example. In another embodiment of the method,

the biomarker is selected from the group consisting of 18FDG, Na18F, 18F-MISO, 18FLT, 18F-Choline, 18F-DOPA and 18F-PSMA, for example. In another embodiment, in the method for producing single or multiple doses of a PET biomarker the bombarding of the one or more target substances can include placing the one or more target substances internally within the compact cyclotron system or placing the one or more target substances externally to the compact cyclotron system. In an embodiment of the method for producing single or multiple doses of one or more (PET) biomarkers, the cyclotron desirably has a beam current in the range of about 1 to about 100 micro-Amperes, for example.

[0030] As used herein, the term "MeV" refers to one mega electron volt, or one million electron volts. One MeV is typically the amount of energy acquired by a charged particle with one electron charge in passing through a potential difference of one million volts in a vacuum. The term "patient" refers to any human or animal subject, particularly including all mammals. The term "radiochemical" is intended to encompass any organic or inorganic compound comprising a covalently-attached radioisotope (e.g., 2-deoxy-2-[^{18}F]fluoro-D-glucose ([18F]FDG)), any inorganic radioactive ionic sodium fluoride solution (e.g., Na[^{18}F]F ionic solution), or any radioactive gas (e.g., "[^{11}C]"), particularly including radioactive molecular imaging probes intended for administration to a patient or subject (e.g., by inhalation, ingestion, or intravenous injection) for human imaging purposes, such probes are referred to also in the art as radiopharmaceuticals, radiotracers, or radioligands. These same probes are also useful in other animal imaging. The term "18F-MISO" refers to [^{18}F] fluoro-2-hydroxypropyl)-2-nitroimidazole. The term "18FLT" refers to Fluorothymidine F-18, which is a tumor-specific PET tracer and radiopharmaceutical. The term "18F-choline" refers to a radioactive substance with the chemical formula 18F-[(CH 3) 3NCH 2CH 2OH]. The term "18F-DOPA" refers to

Fluoro-dihydroxyphenylalanine routinely used in Positron Emission Computed Tomography (PET/CT) in oncologic and nononcologic imaging. The term "18F-PSMA" refers to 18F-Prostate-specific membrane antigen. The term "NH2-N13" is a modified ammonia that has a 13N isotope as the nitrogen atom.

[0031] As used herein, the term, "reagent" is a substance used in synthesizing the biomarker because of the chemical or biological activity of the substance. Examples of a reagent include a solvent, a catalyst, an inhibitor, a biomolecule, and a reactive precursor. The term "reactive precursor" refers to an organic or inorganic non-radioactive molecule that, in synthesizing a biomarker or other radiochemical, is reacted with a radioactive isotope (radioisotope), typically by nucleophilic substitution, electrophilic substitution, or ion exchange. The nature of the reactive precursor varies and depends on the physiological process that has been selected for imaging. Exemplary organic reactive precursors include sugars, amino acids, proteins, nucleosides, nucleotides, small molecule pharmaceuticals, and derivatives thereof. The term "synthesis" refers to the production of the biomarker by the union of chemical elements, groups, or simpler compounds, or by the degradation of a complex compound, or both. Synthesis, therefore, includes any tagging or labeling reactions involving the radioisotope and any processes (e.g., concentration, evaporation, distillation, enrichment, neutralization, and purification) used in producing the biomarker or in processing the target substance for use in synthesizing the biomarker.

[0032] The term "unit dose" refers to the quantity of radioactivity, expressed in millicuries (mCi), which is administered for PET to a particular class of patient or subject. For example, a human adult generally requires a unit dose of biomarker in the range of approximately ten (10) mCi to approximately fifteen (15) mCi. In another example, a unit dose

for a small animal, such as a mouse, may be only a few microcuries (μCi). A unit dose of biomarker necessarily comprises a unit dose of a radioisotope. The term "multi-dose" refers to multiple unit doses of the biomarker.

[0033] As used herein, "microreactors" and "microfluidic chips" refer broadly to small volume reaction systems including microscale, nanoscale, and Pico scale systems. The term "microreactor" is a miniaturized reaction system fabricated, at least in part, using methods of microtechnology and precision engineering. The first prototype microreactors for chemical processes, including chemical synthesis, were manufactured and tested in the early 1990s. The characteristic linear dimensions of the internal structures of a microreactor, such as fluid channels, generally are in the nanometer to millimeter range. For example, the fluid channels in a microreactor typically have a diameter of between approximately a few nanometers and approximately a few millimeters. The length of such channels, however, can vary significantly, *i.e.*, from on the order of millimeters to on the order of meters, depending on the function of the channel. There are exceptions, however, and microreactors having characteristic linear dimensions that are shorter or longer have been developed. A microreactor may include only one functional component, and that component may be limited to a single operation, such as mixing, heat exchange, or separation. Examples of such functional components include micropumps, micromixers, and micro heat exchangers. As more than one operation generally is necessary to perform even the simplest chemical process, more complex systems, sometimes referred to as integrated micro reaction systems, have been developed. Typically, such a system includes at least several different functional components, and the configuration of such systems can vary significantly depending on the chemical process that the system is engineered to

perform. Additionally, integrated micro reaction systems that include arrays of microreactors have been developed to provide continuous-flow production of chemicals.

[0034] The term "microfluidic chips" as used herein refers to fluidic devices that are analogous to electronic integrated circuits fabricated using large-scale integration. As is common in the terminology of emerging scientific or engineering disciplines, there is no unanimity on a definition of microfluidics, and there likely is at least some overlap between microfluidics and the discipline of micro reaction technology described previously. Generally, a microfluidic system is distinguishable in that it processes fluids on a chip that defines a fluidic circuit, where the chip is under digital control and the fluid processing is performed using the fluidic circuit, which includes at least one reaction channel, chamber, compartment, reservoir, vessel, or cleft having at least one cross-sectional dimension (e.g., diameter, depth, length, width, height) on the order of micrometers, nanometers, or even picometers for altering fluid behavior and, possibly, chemical behavior for the purpose of enhancing performance. Accordingly, a microfluidic system enjoys the advantages inherent in a micro-reaction system that were set forth previously. At least some microfluidic systems can be thought of as including a fluidic chip that incorporates a microreactor.

[0035] As to a proton cyclotron for biomarker generator systems, U.S. Patent Nos. 7,476,883 and 8,080,815 to Nutt, and U.S. Patent No. 11,135,321B2 to Khachaturian incorporated by reference herein in their entirety, disclose compact cyclotrons suitable for producing biomarkers including a radiochemical synthesis subsystem for producing a unit dose of a biomarker. These three U.S. patents are incorporated herein by reference in their entirety and, for example, include features that can be adapted for use in the cyclotron apparatuses and

methods of the various embodiments described herein using the guidance of the instant disclosure.

[0036] Referring now to the drawings in greater detail, an exemplary biomarker generator cyclotron system **100** such as a proton cyclotron system **100** such as for the production of a biomarker, has an energy typically in a range of from 7 MeV to 11 MeV and has a beam, the biomarker generator cyclotron system **100** being diagrammatically illustrated in FIG. 2. As illustrated in FIG. 2, the biomarker generator system **100** includes a compact cyclotron that integrates a cyclotron **104**, which is self-shielded, and a target processing and synthesis system **114** or **112**, which can be positioned next to the cyclotron **104**. The cyclotron **104** includes a proton ion source **101**, which is accelerated by an accelerator **108** by magnets **106**, **116** to form a proton beam envelope **102** which can be directed to multiple internal production targets **110** and **109**, such as liquid targets **110** and **109**, for example. The compact cyclotron system can be positioned near a PET/CT imaging device for use "on demand", for example.

[0037] Referring now with reference to FIG. 3, another embodiment of a cyclotron **200**, of the present invention is schematically illustrated. The hydrogen ion source **210** is accelerated using the magnet hills **202** in a RF cavity **204** forming a beam envelope **212** before being focused onto multiple beam targets **206** and **208** positioned opposite other targets **207** and **209**, for example. The beam envelope **212** can be directed, such as by using computer control or computer controls, into multiple beam lines to impact multiple targets, such as targets **207** and **209** simultaneously that can be in a liquid or a gaseous state, for example. In other words, the targets **207** and **209** can access different portions of the beam envelope **212**. For example, the internal target system can include a stainless steel tube having a target window opening centered in the path of the charged particle beam, such as illustrated in US Patent 8,080,815 B2 to Nutt,

which is incorporated herein by reference in its entirety. The beam energy typically can be in the range of 7 MeV to 11 MeV and, in some instances, the cyclotron can be modified, using the guidance of the instant disclosure, to produce energies greater than 11 MeV up to 15 MeV, for example, with varying beam currents of 1 to 100 micro-Amperes, depending on the desired radiochemical production target.

[0038] In an another embodiment, a single or multiple extraction from different sides of the cyclotron **200** can be configured for the cyclotron **200** to serve more than one beamline and be directed to single or multiple external targets simultaneously. For example, the beam line **214** can be extracted and focused using a collimator **213** at any extraction point on the side of the cyclotron **200** to bombard an external target **215** located outside of or externally to the cyclotron **200**. Additionally, target irradiation stations can be placed in independent shielded compartments allowing service without disrupting cyclotron operation. As such, the inventive compact cyclotron system **200** has a dual capability of irradiating a plurality of targets positioned within or outside of the cyclotron **200** which can be in a gaseous, a liquid or a solid state for the production of a multitude of radioisotopes, simultaneously or non-simultaneously, including but not limited to F-18, C-11, N-13, Ga-68, Zr-89, Tc-99m, C-11, N-13, O-15, Cu-64, Ga-67, In-111, I-123, AC-225 and Pd-103, for example.

[0039] The typical dimensions of the exemplary cyclotron, such as the cyclotron **200**, according to the present invention, can have a diameter of 49 inches and a height of 42 inches, lower shields, having a diameter of 8 feet and height of 27 inches, floor shielding having a diameter of 48 inches and height of 14 inches, and top movable shields having a diameter of 8 feet and height of 37 inches, for example. The shield material can be made from ceramic/polymer composite material, for example, that can absorb all ionizing radiation. As

such, the cyclotron, such as the cyclotron **200**, can be placed near a PET/CT scan table in a hospital room or a clinic without causing harmful radiation problems.

[0040] FIG. 4 illustrates an embodiment of the improved biomarker generator system or cyclotron system **300**, including a cyclotron **309** and one or more of a radiopharmaceutical micro-synthesis system **316** and a radiopharmaceutical macro-synthesis system **317**. As shown in FIG. 4, the exemplary cyclotron **309** is a dual capability system capable of producing small scale as well as larger scale radiochemicals. In an embodiment, this inventive cyclotron system is housed in a cyclotron room (identified in FIG.4 as a "CYCLOTRON ROOM") separated from a GMP (good manufacturing practice) room (identified in FIG.4 as a "GMP ROOM"), such as in a hospital or a laboratory setting. The CYCLOTRON ROOM comprises the cyclotron **309**, attached to the floor using hydraulic jacks **310**, a controller **308** as can be associated with, integral with or in communication with a computer controller system or computer **315** or other suitable processor, the controller **308** and/or computer **315** having programming or software to control the operation and performance of the cyclotron **309** and to control operation and performance of the radiopharmaceutical micro-synthesis system **316** and/or the radiopharmaceutical macro-synthesis system **317;** and, in communication with the cyclotron **309**, a cyclotron chiller **302** to cool the cyclotron **309**, and various gas lines **301**, a water manifold **303**, and gas valves **304** for gases and liquids used in operation of the cyclotron **309**, the radiopharmaceutical micro-synthesis system **316** and/or the radiopharmaceutical macro-synthesis system **317**. The cyclotron **309** is fully self-shielded by a shielding system **312** that absorbs nearly all the ionizing radiation produced by the proton beam generated by the cyclotron **309**. The shield **312** around the cyclotron **309**, which in some embodiments is less than 8 feet in diameter, facilitates reducing the radiation field around the cyclotron **309** to such a level that it is

safe for a radiation worker to be present (typically <1 mrem/hr) in the workspace around cyclotron **309** including the accelerator, such accelerator, for example, being illustrated in and described with reference to the cyclotron **100** of FIG. 2 and the cyclotron **200** of FIG. 3. The shield **312** can be made, for example, from polymer/ceramic composite material, or other suitable material, to absorb nearly all ionizing radiation generated from the cyclotron **309**.

[0041] Additionally, the beam line or envelope of the cyclotron **309** can be directed to an external target **314**, situated on the side of the cyclotron **309**, for example. The cyclotron **309,** the radiopharmaceutical micro-synthesis system **316** and the radiopharmaceutical macro-synthesis system **317** are respectively configured to receive chemical reagents and/or one or more radioactive substances for radioisotope production, such as via conveyor belts or tubes **305**, **306** and **307**, or by other the suitable conveyances. Once the radioisotopes are produced by irradiation of targets or target substances to provide the radioactive substance(s), the radioisotope(s) travel(s) to a self-shielded chemical production module (CPM), such as to the radiopharmaceutical micro-synthesis system **316** situated next to the cyclotron **309** or travel to the radiopharmaceutical macro-synthesis system **317** inside a fully shielded GMP (good manufacturing practice) room ("GMP ROOM") illustrated and identified in FIG 4 for a larger scale multi-dose radiochemical synthesis for transportation to outside labs and hospitals.

[0042] The CPM, such as the radiopharmaceutical micro-synthesis system **316** situated within the CYCLOTRON ROOM and the radiopharmaceutical macro-synthesis system **317** in the GMP ROOM, holds reagents and solvents that are required during the radiopharmaceutical synthesis process. In the radiopharmaceutical micro-synthesis system **316** or in the radiopharmaceutical macro-synthesis system **317**, the radiopharmaceutical solution is synthesized from the radioisotope and then purified for testing and administration. In some

embodiments, following synthesis and purification, a quality control can be performed of the radiopharmaceutical, which is readily apparent to those skilled in the art.

[0043] The computer **315** in conjunction with the controller **308** controls systems constituting or associated with the cyclotron **309,** the radiopharmaceutical micro-synthesis system **316,** the radiopharmaceutical macro-synthesis system **317** and/or a quality control system and ensures that these systems are capable of operating simultaneously, non-simultaneously and/or independently to ensure or facilitate the most efficient workflow. The systems can be also configured to accept manual injection, input, or introduction of a radioisotope. The computer **315**, in conjunction with the controller **308**, can also control multiple targets in the cyclotron, such as in the cyclotron **309**, and move them into the beam of the cyclotron independently to produce different radioisotopes from different radioactive substances. In some embodiments, one or more of these systems of the biomarker generator system or cyclotron system **300** can be configured in conjunction with a vacuum pump to optimize the synthesis process and the yield of the radiopharmaceutical.

[0044] Continuing with reference to FIG. 4, the controller **308** in conjunction with the computer or computer controller system **315** is used to control the beam of charged particles, such as a proton beam, and the beam intensity to accurately and precisely deliver the charged particles, such as protons or hydrogen ions, to the internal target radiochemical. The computer controller system **315**, in conjunction or association with the controller **308,** desirably is a single control system for controlling the plurality of the components of the cyclotron system **300**, such as the compact cyclotron **309** to provide the beam, such as a proton beam, of the requisite intensity, current and energy, and to control the radiopharmaceutical synthesis subsystem such as the radiopharmaceutical micro-synthesis system **316** and/or the radiopharmaceutical macro-

synthesis system **317**. The computer controller system **315**, in conjunction or association with the controller **308,** controls all systems and ensures and facilitates operating all systems of the biomarker generator system or cyclotron system **300,** namely the cyclotron, the synthesis system and the quality control system simultaneously, non-simultaneously and/or independently to ensure or facilitate the most efficient workflow. The system can be also configured to accept manual injection, input, or introduction of a radioisotope, such as from the tube **307**. The computer **315**, in conjunction or association with the controller **308,** can also control multiple internal targets in the cyclotron and move them into the beam of the cyclotron independently to produce different radioisotopes. The computer **315**, in conjunction or association with the controller **308,** can also control delivery of the beam, such as consisting essentially of protons, to an external target by directing the beamline to the external target **314**. The computer **315**, in conjunction or association with the controller **308,** can also control and automatically transfer via a conveyor belt or tube **371** the radioisotope produced into the radiopharmaceutical macro-synthesis system **317** for radiochemical/biomarker synthesis.

[0045] In some embodiments of the automated radiopharmaceutical production for automatically producing a unit dose or multiple doses of the radiopharmaceutical includes a user interface integrated with the computer **315,** the user interface enabling the selection of a selected radiopharmaceutical for production, the selection being made on and recorded by the user interface, whereby the user interface communicates an identity of the selected radiopharmaceutical to a computer. A cyclotron, such as the cyclotron **309**, is in communication with the computer **315,** which is in conjunction or association with the controller **308.** The cyclotron produces a radioisotope associated with the selected radiopharmaceutical. The cyclotron initiates production of the radioisotope upon receiving computer activating

instructions; and upon receiving computer activating instructions, such as originating from the computer **315**, the chemical production subsystem transfers, synthesizes, and purifies the radioisotope into a maximum quantity of a radiopharmaceutical on the order of up to ten units or higher doses using a disposable microfluidic radiopharmaceutical synthesis card system, for example.

[0046] The radiochemical synthesis subsystem(s) is/are integrated with or in communication with the cyclotron, which subsystem(s) are desirably fully automated. The cyclotron **309** is desirably configured to be in communication with or integrated with the radiopharmaceutical micro-synthesis system **316,** and the cyclotron **309** is desirably configured to be in communication with or integrated with the radiopharmaceutical macro-synthesis system **317**. Also, the radiochemical synthesis subsystem(s), such as the radiopharmaceutical micro-synthesis system **316** and the radiopharmaceutical macro-synthesis system **317**, include one or more of a microreactor or a microfluidic chip for synthesizing one or more radiochemicals from one or more radioactive substances. Typically, the radiochemical transfer to the chemistry modules **316** and **317,** the radiopharmaceutical micro-synthesis system **316** and the radiopharmaceutical macro-synthesis system **317,** for isolation and separation are automated and fully shielded. While the small-scale chemical synthesis in the chemistry module **316** can be conducted next to the cyclotron **309**, the large-scale chemistry in the chemistry module **317** can be conducted in the adjoining separate GMP ROOM. Advantageously, the radiochemical synthesis system is typically a simple "push button" synthesis system for generating FDG-F18 and NH3-13N radio-chemicals, for example, on an as needed basis in the hospital or clinic setting. The improved biomarker generator allows dual operation using a liquid volume or solid sample of the target radioactive substance that is unusually small in the area of

radiopharmaceutical production. After irradiation, the radioisotope and at least one reagent are transferred to the radiochemical synthesis system, which is desirably fully automated using a computer user interface. The radioisotope undergoes processing as necessary. Ultimately, the radiopharmaceutical micro-synthesis system combines the radioisotope with the reagent or reagents to synthesize the biomarker.

[0047] Table 1 illustrates the nuclide production for a cyclotron system using different nuclides with varying beam conditions, run length and the resulting production yield using embodiments of the inventive cyclotron systems and methods according to the present invention. The exemplary cyclotron is capable of producing the following radionuclides listed in Table 1. It should be noted that the Ga-68 production energy maximum is 12 MeV.

Desired Nuclide	**Yield**					
	GBq/uA hr	mCi/uA hr	Beam Current (I) Conditions (uA)	Yield mCi/hr	Run length Time (hr)	Production Run Yield (mCi)
F-18	2.1	56.7568	15	851.3514	2	1702.7027
Ga-68	1.75	47.2973	15	709.4595	2	1418.9189
Zr-89	1.54E-02	0.41622	30	12.48649	12	149.83784
TC-99m	1.23E-02	0.33243	30	9.972973	12	119.67568
C-11	2.1	56.7568	30	1702.703	1	1702.7027
N-13	0.323	8.72973	30	261.8919	1	261.89189
O-15	2.24	60.5405	15	908.1081	0.5	454.05405
Cu-64	0.237	6.40541	30	192.1622	12	2305.9459
Ga-67	0.275	7.43243	30	222.973	24	5351.3514

In-111	1.38E-02	0.37297	30	11.18919	24	268.54054
I-123	2.79E-02	0.75405	30	22.62162	24	542.91892
Pd-103	2.72E-03	0.07351	30	2.205405	24	52.92973

[0048] Surprisingly and advantageously, embodiments of the inventive cyclotron system of the present invention can produce a yield of F-18 greater than 20 times with a beam current of about 15 micro-Amperes as compared with a conventional prior art cyclotron, such as that illustrated in FIG. 1. The inventive cyclotron of the present invention can accelerate the protons at higher energies of up to 11 MeV, or even up to 15 MeV, and increased proton beam current capabilities up to 100 micro-Amperes, which is capable of producing single or multiple batches of biomarkers including ^{18}FDG, Na^{18}F,^{18}F-MISO, ^{18}FLT, ^{18}F-Choline,^{18}F-DOPA and ^{18}F-PSMA as well as N-13 ammonia, C-11 labelled compounds, Cu64 as well as Ga68 compounds "on demand" even in a small hospital or medical clinic setting. Embodiments of the inventive cyclotron can be configured to irradiate multiple internal and external targets and produce radiochemical at a much higher yield than that of previous prior art or conventional cyclotron systems. The novel design of the multiple targets including the use of amplifier systems of embodiments of this inventive compact cyclotron system allows for the production of higher proton beam current than the prior art cyclotrons thereby enabling the production of a variety of radioisotopes and radiochemicals in a single dose or multi-doses simultaneously by a simple push button interface on a computer, for example.

[0049] Table 2 illustrates the Technetium (Tc99m) production capabilities using embodiments of the inventive cyclotron of the present invention.

Energy (Mev)	Irradiation Time (hr)	Beam Current Micro Amperes	Yield in Bq	Yield in mCi
9	8	30	1.38E +09	3.74E+01
11	8	30	1.26E +10	3.39+02
15	8	150	7.20E+10	1.95E+03

[0050] As is evident from the Table 2, embodiments of the inventive cyclotron are capable of producing Technetium (Tc99m) at higher yields by increasing the energy and the beam energy and current. Technetium (Tc-99m) is an isotope highly desired in a number of medical diagnostic imaging scans, such as Tc99m is used as a radioactive tracer for nuclear medicine such as using SPECT/CT (single photon emission computed tomography/computed tomography). Thus, embodiments of the inventive cyclotron are versatile in producing several radioisotopes simultaneously for imaging, and believed to be advantageous over various prior art cyclotrons. In various embodiments, the inventive cyclotron can be modified to produce higher proton beam energies up to 15 MeV for producing higher quantities of Technetium (Tc-99m), for example.

[0051] In an embodiment of the inventive biomarker generator system, a biomarker generator system **400** allows for the nearly on-demand and automated production of approximately one (1) unit dose or multiple unit doses of the biomarker via the schematic illustration depicted in FIG. 5. A micro-accelerator cyclotron **401** produces a beam of charged particles that bombards target substances to create a precursory unit or multiple doses of a

radioisotope **402**. In the next step, the radioisotope is transferred to the radiopharmaceutical synthesis system **404** within the cyclotron room or is transferred to a large scale radiopharmaceutical synthesis system in a GMP room **405**, which is an automated chemical module, where it is mixed with reagents **403** to create either a small dose **407** such as a unit dose or large multi doses **406** of the biomarker depending upon the need of the clinic or hospital.

[0052] Referring now to FIG. 6, embodiments of the inventive biomarker generator system allows for the nearly on-demand production of approximately one unit dose or multiple unit doses of biomarker via the schematic illustration **500** depicted. The method of generating a unit dose or multi-doses of biomarker comprises several steps. A compact cyclotron **501** is provided which generates charged particles in a vacuum **502**. The charged particles are accelerated along a path forming a beam envelope of charged particles **503**. The ion beam of charged particles is used to bombard a plurality of targets positioned within or outside of the cyclotron, the targets can be solid, or can also be in a liquid or a gaseous state, with the beam thereby producing a radioisotope that is transformed into a radioisotope-containing solution having an activity of less than, or equal to, approximately sixty (60) mCi **504**. The radioisotope-containing solution is transferred to a micro-reaction (or microfluidic) subsystem **505**. Other chemical reagents may be added to this solution. The radioisotope is concentrated yielding a concentrated radioisotope-containing solution **506** which can be used to synthesize approximately one unit dose or multiple unit doses of PET biomarker using the concentrated radioisotope-containing solution **507**. The entire process is desirably computer controlled and is typically fully automated. Advantageously, the embodiments of the inventive cyclotron system are capable of selecting the type of radiochemical production typically by a simple "push-button"

user interface to select either FDG-F-18 or NH2-N13 production, for example, on an as needed basis.

[0053] In another embodiment, after the radioisotope is isolated, the micro-accelerator and the radiochemical synthesis subsystem with the regents, together in the same system, enable the generation of a unit dose or multiple unit doses of the radioisotope in combination with the synthesis of a unit dose or unit doses of the biomarker. Microreactors and microfluidic chips typically perform their respective functions in less than fifteen (15) minutes, some in less than two (2) minutes. One skilled in the art will recognize that a radiochemical synthesis subsystem having at least one microreactor and/or microfluidic chip is flexible and may be used to synthesize a biomarker other than FDG-F18, including a biomarker that is labeled with a radioisotope other than fluorine-18, such as carbon-11, nitrogen-13, or oxygen-15, Cu 64 etc. One skilled in the art will recognize also that such a subsystem may comprise parallel circuits, enabling simultaneous production of a unit dose or multiple unit doses of a variety of biomarkers.

[0054] Because the half-lives of the radioisotopes (and, hence, the biomarkers) most suitable for safe molecular imaging of a living organism are limited, e.g., the half-life of fluorine-18 is 110 minutes, nearly "on-demand" production of multiple doses of biomarkers presents a significant advancement for both clinical medicine and biomedical research. The present invention aims to provide larger amounts of 18F radioisotope that could lead to multiple doses of [18F] FDG "on-demand" with greater efficiency, for example, which is viable even for small hospitals and clinics as compared with various prior art systems.

[0055] Embodiments of the inventive compact biomarker generator cyclotron system can also produce other positron emitting isotopes, such as F-18, C-11, N-13, O-15, Cu-64, Ga-67, In-111, I-123, Ac-225, Pd-103 and Ga-68, depending on various industrial and biomedical research applications. Embodiments of the inventive compact cyclotron system are advantageously compact as they can be typically installed in a spacing of 5 meters by 5 meters, can be self-shielded and can be placed in any spacing near an imaging device such as the PET/CT table. Also, embodiments of the inventive compact cyclotron system are relatively easy to maintain, and are relatively cost effective, thereby making medical isotope and biomarker generating of a single dose or multiple doses "on-demand" useful for a variety of applications even for in house biomarker generation and for small regional hospitals. Also, embodiments of the inventive compact biomarker generator cyclotron system can generate radio-chemically pure, clinical grade radiotracers and radiopharmaceuticals ready for use in humans, animals and other mammals "on-demand" and for *in vitro* and *in vivo* biomedical research applications. Advantageously, the inventive cyclotron system is desirably fully automated for radiochemistry and for quality control testing evaluation. The relative reduced cost and relative reduced infrastructure requirements of the compact micro-accelerator compared to various known cyclotrons, coupled with the built-in automated radio-chemistry synthesis subsystem having at least one or more of a microreactor and/or a microfluidic chip facilitates making in house biomarker generation a viable, efficient option for small clinics and hospitals Moreover, embodiments of the inventive cyclotron system can be advantageous for nuclear cardiology/oncology applications, for example.

[0056] It is to be understood that the embodiments of the inventive cyclotron apparatuses, systems and methods taught and described in terms of the beam of charged

particles, such as a proton beam or a negative hydrogen ion (H-) beam, with internal and external targets for the production of radioisotopes and biomarkers are illustrative, and the beam of charged particles used can depend on the use, method, and application, and should not be construed in a limiting sense.

[0057] It is to be understood that the present invention is not limited to the embodiments described above but encompasses any and all embodiments within the scope of the following claims.

WE CLAIM:

1. A compact, self-shielded cyclotron system for producing a radiochemical, said cyclotron system comprising:

a cyclotron for generating a beam of charged particles having a beam envelope consisting essentially of particles having an energy in a range of 7 MeV to 11 MeV;

an accelerator for directing the beam of charged particles along a path;

a plurality of targets positioned one or more of within or outside of said cyclotron, said plurality of targets positioned in the path of the beam of charged particles, said plurality of targets comprising one or more target substances each having a composition selected for producing one or more radioactive substances during interaction with the beam of charged particles, wherein each of said one or more target substances is in a solid, a gaseous or a liquid state; and

a radiochemical synthesis subsystem integrated with or in communication with said cyclotron, said radiochemical synthesis subsystem having one or more of a microreactor or a microfluidic chip, said radiochemical synthesis subsystem for receiving the one or more radioactive substances, for receiving at least one reagent to synthesize corresponding one or more radiochemicals and for synthesizing the one or more radiochemicals.

2. The compact, self-shielded cyclotron system for producing a radiochemical according to claim 1, wherein said cyclotron has a beam current in a range of about 1 to about 100 micro-Amperes.

3. The compact, self-shielded cyclotron system for producing a radiochemical

according to claim 1, wherein said plurality of targets each comprises a plurality of liquid internal targets positioned within or external to said cyclotron.

4. The compact, self-shielded cyclotron system for producing a radiochemical according to claim 1, wherein said plurality targets each comprises a solid or a gaseous target positioned within or external to said cyclotron.

5. The compact, self-shielded cyclotron system for producing a radiochemical according to claim 1, further comprising:

a beam collimator to direct the beam of charged particles to a solid or a gaseous target of said plurality of targets positioned external to or outside of said cyclotron.

6. The compact, self-shielded cyclotron system for producing a radiochemical according to claim 1, wherein said cyclotron system comprises a shield positioned externally to surround said cyclotron to reduce a radiation field generating from the beam of charged particles to an acceptable level of less than 1 millirem/hr.

7. The compact, self-shielded cyclotron system for producing a radiochemical according to claim 1, wherein the beam of charged particles consists essentially of protons having an energy of approximately 7 MeV to 11 MeV.

8. The compact, self-shielded cyclotron system for producing a radiochemical according to claim 1, further comprising:

a computer controller system configured in communication with said cyclotron and said radiochemical synthesis subsystem to control said cyclotron to generate and deliver the beam of

charged particles for irradiation of said plurality of targets and to control said radiochemical synthesis subsystem.

9. The compact, self-shielded cyclotron system for producing a radiochemical according to claim 8, wherein the computer controller system comprises a user interface to enable selection of one or more radiopharmaceuticals for radiochemical synthesis by said radiochemical synthesis subsystem.

10. The compact, self-shielded cyclotron system for producing a radiochemical according to claim 9, wherein the user interface receives a selection input for the radiochemical synthesis of the one or more radiochemicals, the one or more radiochemicals selected from the group consisting of FDG-F18 or NH2-N13.

11. The compact, self-shielded cyclotron system for producing a radiochemical according to claim 1, wherein said accelerator includes a permanent magnet for directing the beam of charged particles as the beam of charged particles is being accelerated by said accelerator.

12. The compact, self-shielded cyclotron system for producing a radiochemical according to claim 1, wherein the one or more radioactive substances each includes a radioisotope that emits positrons and wherein the radioisotope that emits positrons is a positron emission tomography (PET) biomarker.

13. The compact, self-shielded cyclotron system for producing a radiochemical according to claim 12, wherein the PET biomarker is selected from the group consisting of F-18, C-11, N-13, Ga-68, O-15, Cu-64, Ga 67, In-111, I-123, Zr-89, Tc-99m, Pd-103 and Ac-225.

14. The compact, self-shielded cyclotron system for producing a radiochemical according to claim 1, wherein each of the one or more radiochemicals is substantially radiochemically pure to provide a radiochemical that is ready for use in patients and *in-vitro* and *in-vivo* applications.

15. The compact, self-shielded cyclotron system for producing a radiochemical according to claim 1, wherein the beam of charged particles has an energy of approximately 7 MeV to 15 MeV.

16. The compact, self-shielded cyclotron system for producing a radiochemical according to claim 1, wherein the beam of charged particles consists essentially of protons having an energy of approximately 7 MeV to 15 MeV.

17. A compact, self-shielded cyclotron system for producing a radiochemical, said cyclotron system comprising:

a cyclotron for generating a beam of charged particles having a beam envelope consisting essentially of particles having an energy in a range of 7 MeV to 11 MeV;

an accelerator for directing the beam of charged particles along a path,

wherein said cyclotron is configured to provide the beam of charged particles to interact with a plurality of targets positioned one or more of within or outside of said cyclotron in the path of the beam of charged particles, said plurality of targets comprising one or more target substances each having a composition selected for producing one or more radioactive substances during interaction with the beam of charged particles, each of said one or more target substances is in a solid, a gaseous or a liquid state; and

a radiochemical synthesis subsystem integrated with or in communication with said cyclotron, said radiochemical synthesis subsystem having one or more of a microreactor or a microfluidic chip, said radiochemical synthesis subsystem for receiving the one or more radioactive substances, for receiving at least one reagent to synthesize corresponding one or more radiochemicals and for synthesizing the one or more radiochemicals.

18. The compact, self-shielded cyclotron system for producing a radiochemical according to claim 17, wherein the beam of charged particles has an energy of approximately 7 MeV to 15 MeV.

19. The compact, self-shielded cyclotron system for producing a radiochemical according to claim 17, wherein the beam of charged particles consists essentially of protons having an energy of approximately 7 MeV to 15 MeV.

20. A method for producing a single dose or multiple doses of one or more positron emission tomography (PET) biomarkers, said method comprising the steps of:

(a) providing a compact cyclotron system for generating a beam of charged particles, the beam consisting essentially of protons having an energy in a range of 7 MeV to 11 MeV;

(b) generating the beam of charged particles consisting essentially of protons using a particle accelerator associated with said cyclotron system;

(c) bombarding one or more target substances with the beam consisting essentially of protons to produce one or more radioactive substances corresponding to one or more of the target substances;

(d) providing a radiochemical synthesis subsystem having one or more of a microreactor or a microfluidic chip, said radiochemical synthesis subsystem for receiving the one or more radioactive substances, for receiving at least one reagent to synthesize the one or more radioactive substances, and for synthesizing from the one or more radioactive substances one or more unit doses of the one or more PET biomarkers corresponding to the one or more radioactive substances synthesized by said radiochemical synthesis subsystem;

(e) transferring the one or more radioactive substances to said radiochemical synthesis subsystem;

(f) transferring the at least one reagent to said radiochemical synthesis subsystem; and

(g) synthesizing the one or more unit doses of the one or more PET biomarkers by said radiochemical synthesis subsystem.

21. The method for producing a single dose or multiple doses of one or more PET biomarkers according to claim 20, further comprising the step of:

controlling by a computer controller the synthesis of the one or more unit doses of the one or more PET biomarkers.

22. The method for producing a single dose or multiple doses of one or more PET biomarkers according to claim 20, wherein the one or more radioactive substances comprise one or more positron-emitting substances selected from the group consisting of F-18, C-11, N-13, Ga-68, O-15, Cu-64, Ga 67, In-111, I-123, Zr-89, Tc-99m, Pd-103 and Ac-225.

23. The method for producing a single dose or multiple doses of one or more PET

biomarkers according to claim 20, wherein each of the one or more PET biomarkers is selected from the group consisting of 18FDG, Na18F, 18F-MISO, 18FLT, 18F-Choline, 18F-DOPA and 18F-PSMA.

24. The method for the producing a single dose or multiple doses of one or more PET biomarkers according to claim 20, wherein bombarding the one or more target substances comprises one or more of placing the one or more target substances internally within said cyclotron system or placing the one or more target substances externally to said cyclotron system.

25. The method for the producing a single dose or multiple doses of one or more PET biomarkers according to claim 20, wherein said cyclotron system has a beam current in a range of about 1 to about 100 micro-Amperes.

26. The method for the producing a single dose or multiple doses of one or more PET biomarkers according to claim 20, wherein the beam of charged particles consists essentially of protons having an energy of approximately 7 MeV to 15 MeV.

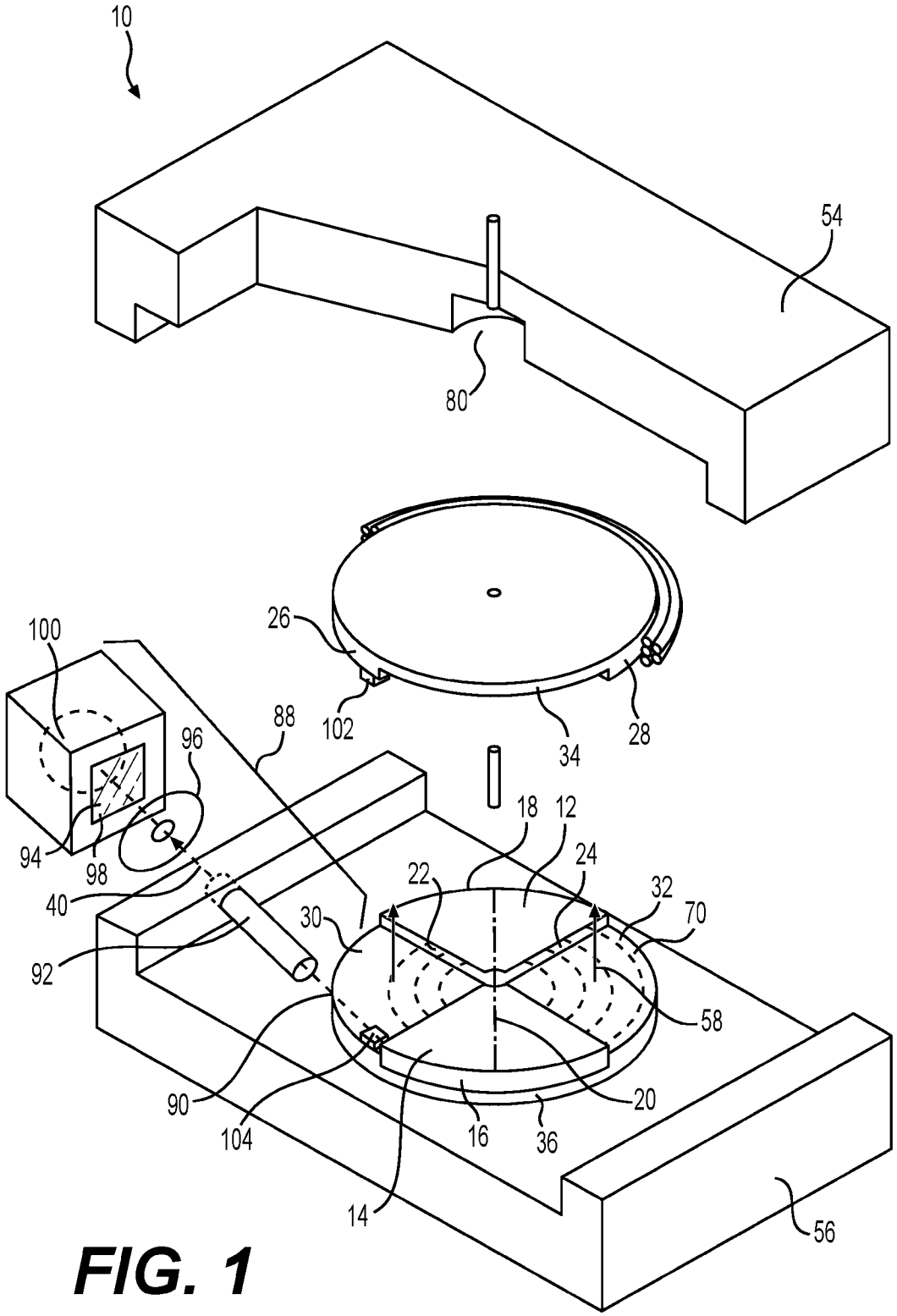

FIG. 1
(PRIOR ART)

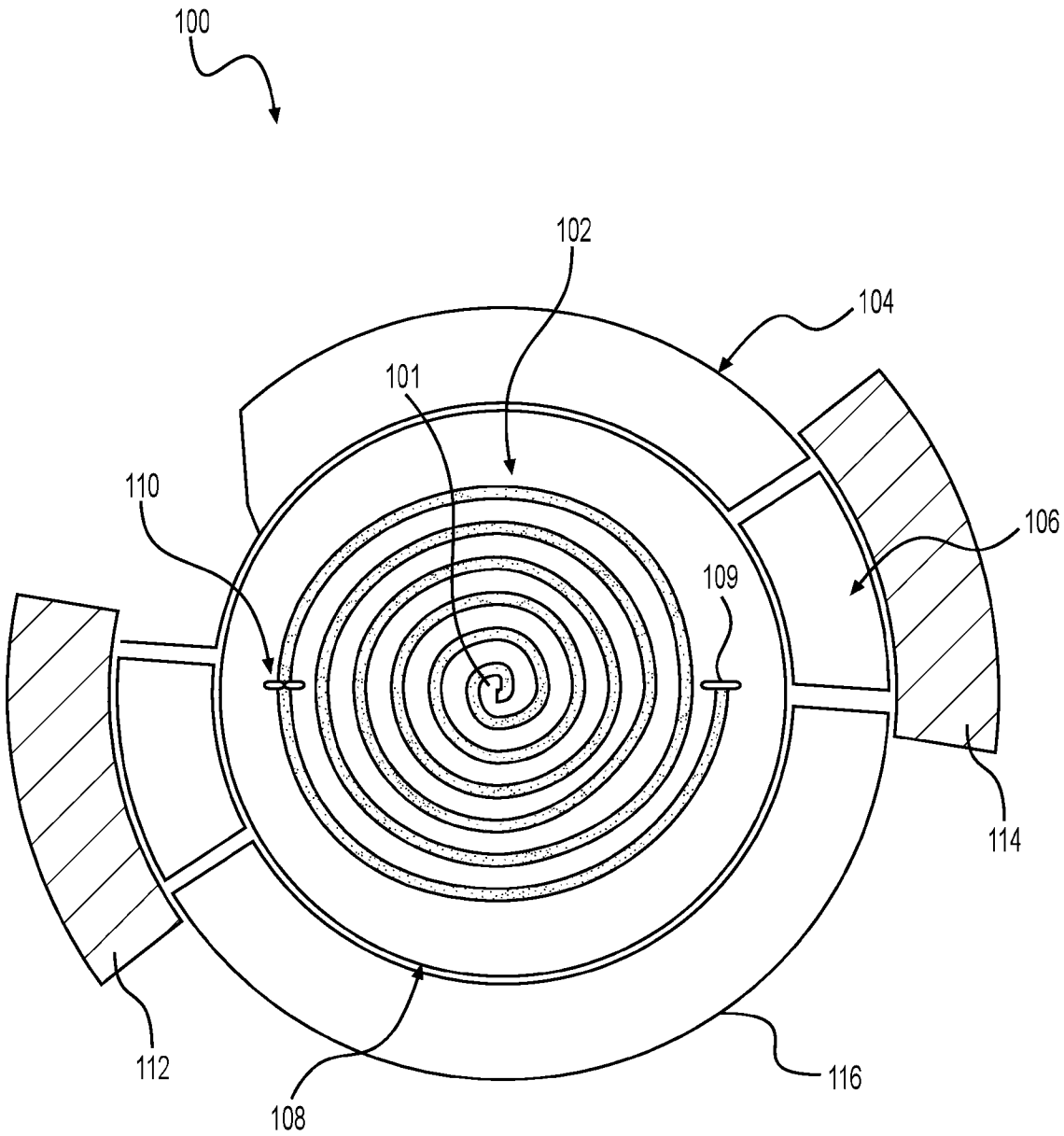

FIG. 2

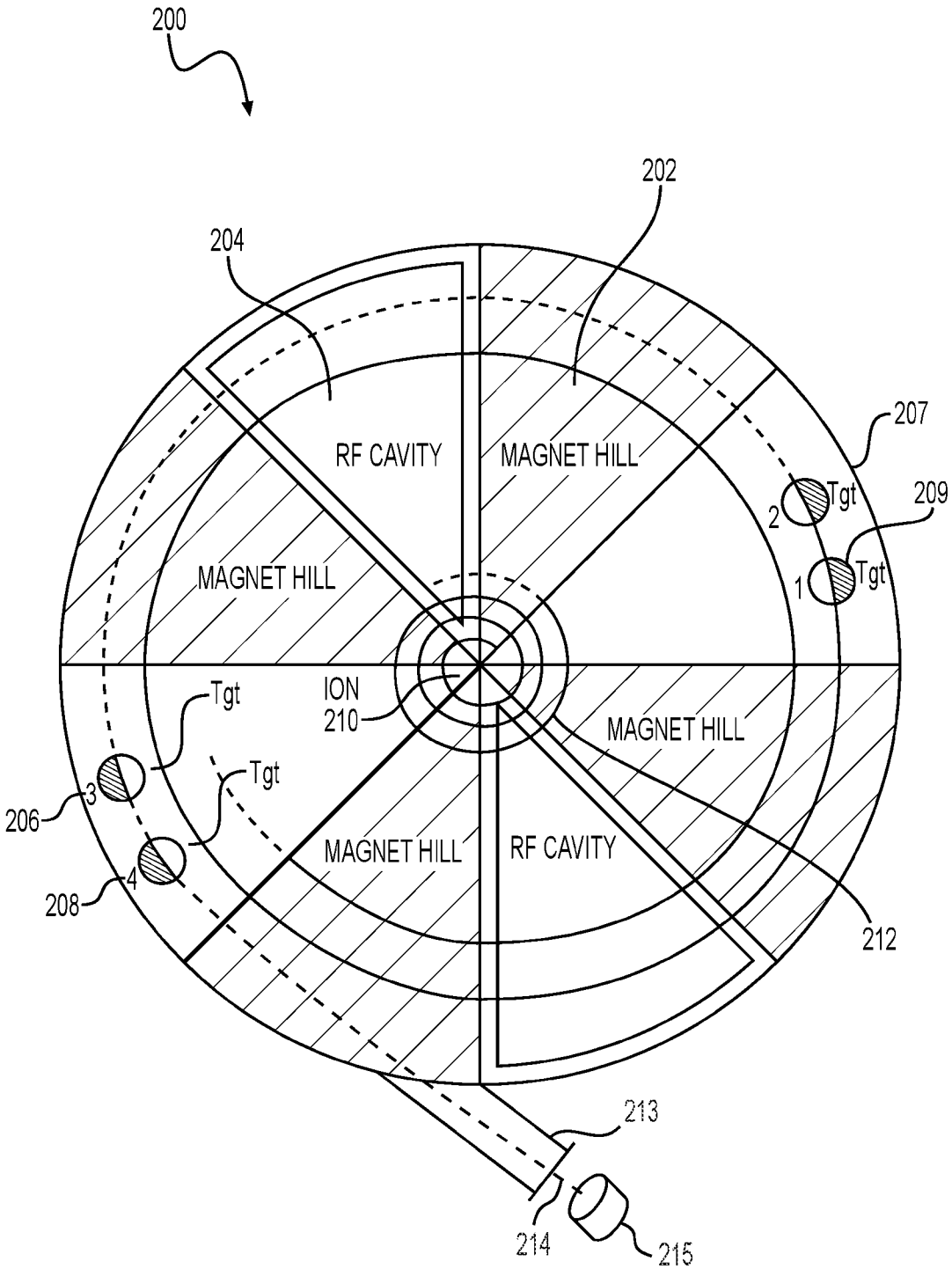
200
202
204
RF CAVITY
MAGNET HILL
207
209
Tgt
2
Tgt
1
MAGNET HILL
Tgt
ION
210
MAGNET HILL
Tgt
206
3
4
208
MAGNET HILL
RF CAVITY
212
213
214
215

FIG. 3

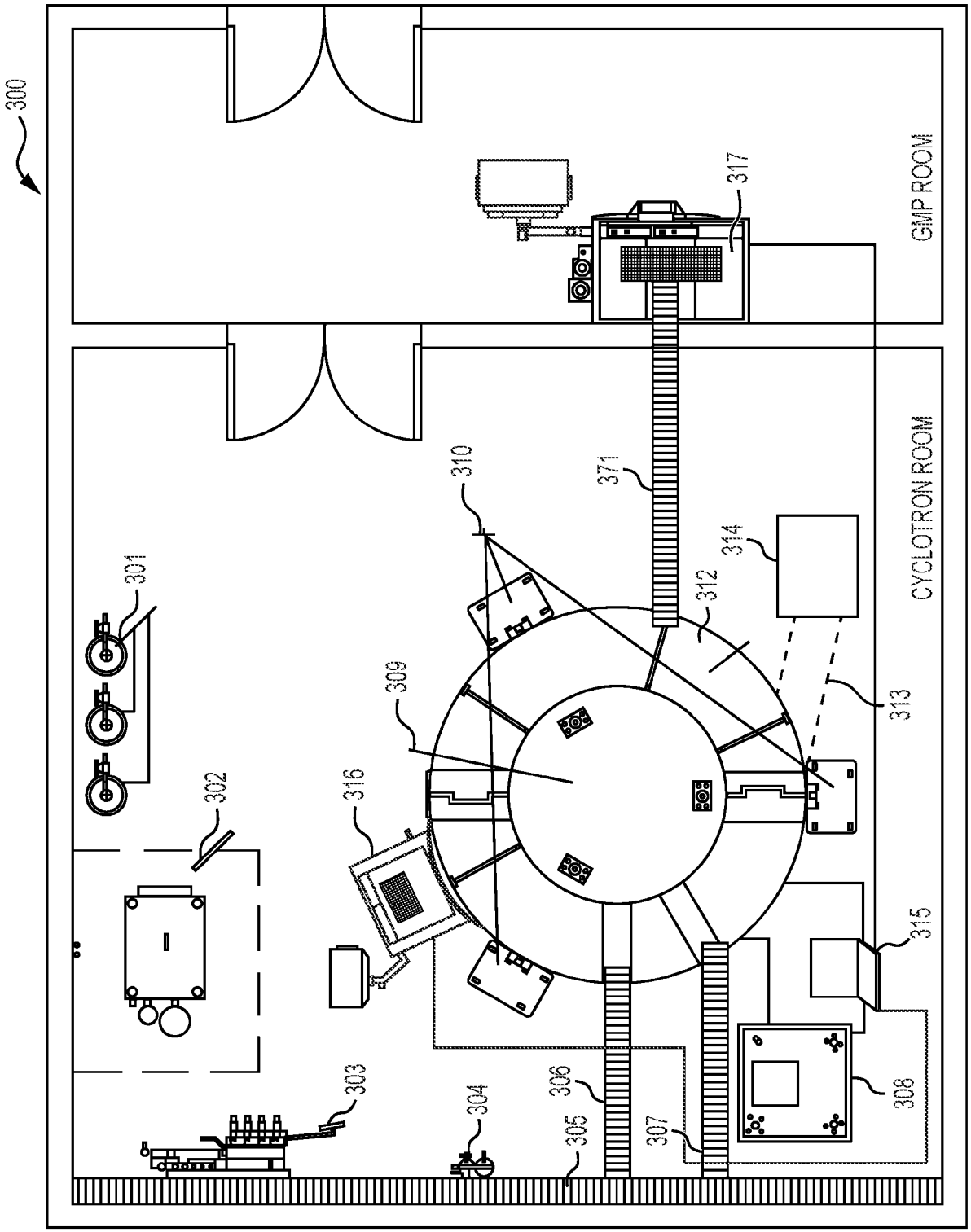
300
GMP ROOM
CYCLOTRON ROOM
317
310
371
314
312
313
309
316
301
302
303
304
305
306
307
308
315

FIG. 4

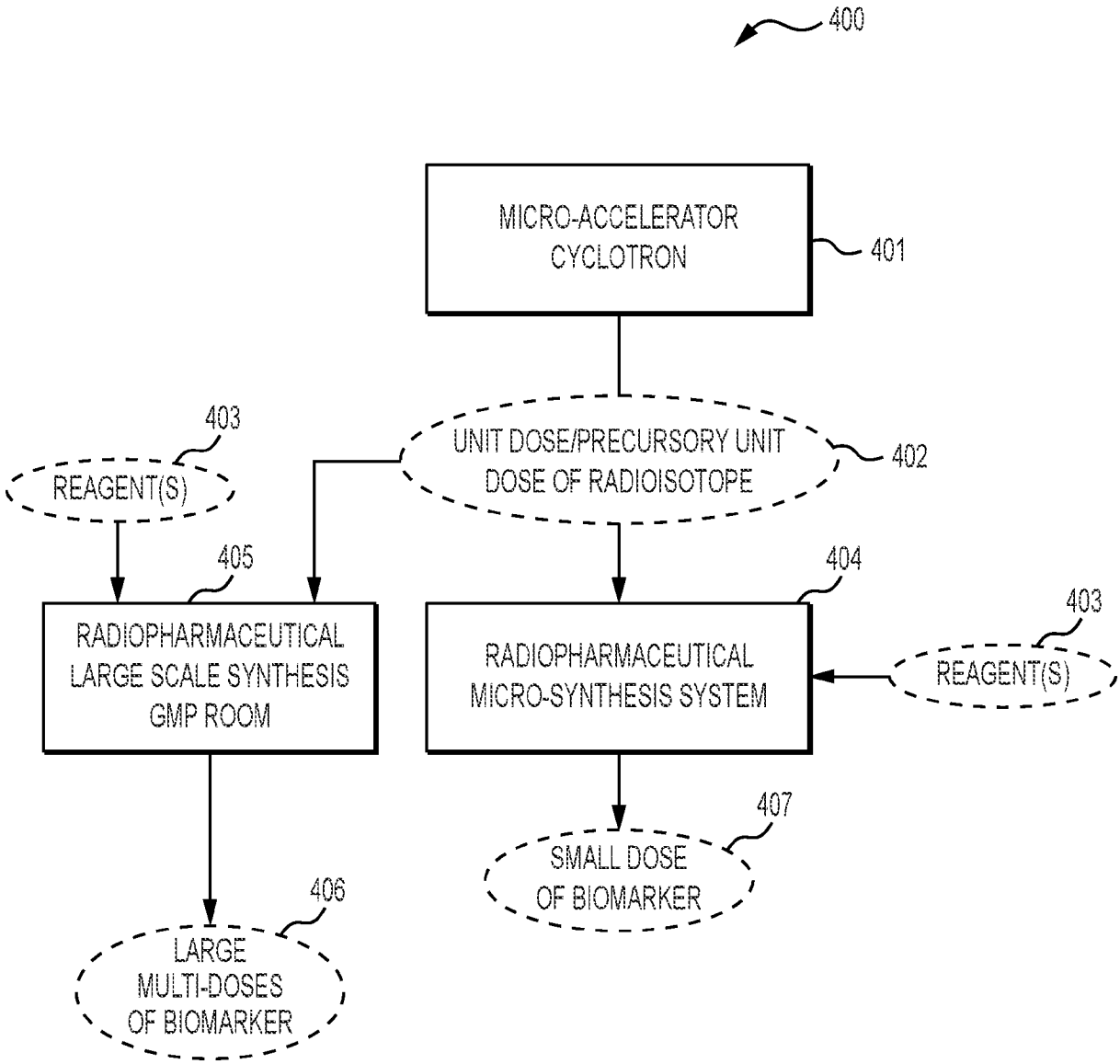
400
MICRO-ACCELERATOR CYCLOTRON
401
UNIT DOSE/PRECURSORY UNIT DOSE OF RADIOISOTOPE
402
403
REAGENT(S)
405
RADIOPHARMACEUTICAL LARGE SCALE SYNTHESIS GMP ROOM
404
RADIOPHARMACEUTICAL MICRO-SYNTHESIS SYSTEM
403
REAGENT(S)
406
LARGE MULTI-DOSES OF BIOMARKER
407
SMALL DOSE OF BIOMARKER

FIG. 5

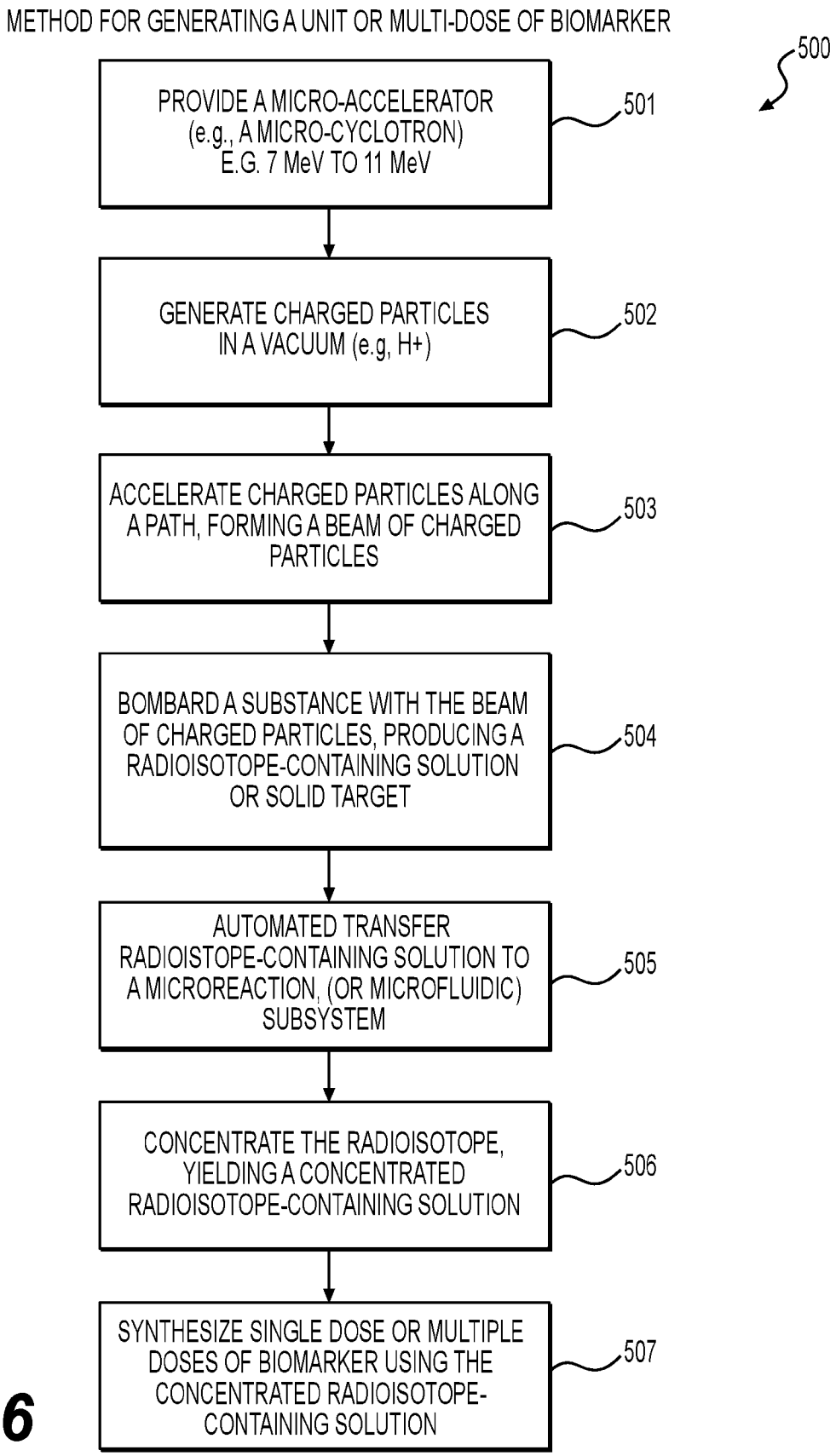
METHOD FOR GENERATING A UNIT OR MULTI-DOSE OF BIOMARKER
500
PROVIDE A MICRO-ACCELERATOR (e.g., A MICRO-CYCLOTRON) E.G. 7 MeV TO 11 MeV
501
GENERATE CHARGED PARTICLES IN A VACUUM (e.g, H+)
502
ACCELERATE CHARGED PARTICLES ALONG A PATH, FORMING A BEAM OF CHARGED PARTICLES
503
BOMBARD A SUBSTANCE WITH THE BEAM OF CHARGED PARTICLES, PRODUCING A RADIOISOTOPE-CONTAINING SOLUTION OR SOLID TARGET
504
AUTOMATED TRANSFER RADIOISTOPE-CONTAINING SOLUTION TO A MICROREACTION, (OR MICROFLUIDIC) SUBSYSTEM
505
CONCENTRATE THE RADIOISOTOPE, YIELDING A CONCENTRATED RADIOISOTOPE-CONTAINING SOLUTION
506
SYNTHESIZE SINGLE DOSE OR MULTIPLE DOSES OF BIOMARKER USING THE CONCENTRATED RADIOISOTOPE-CONTAINING SOLUTION
507

FIG. 6