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(54) Title: RADIONUCLIDE GENERATOR HAVING FIRST AND SECOND ATOMS OF A FIRST ELEMENT

(57) Abstract: The invention is in the field of a radionuclide generator. A radionuclide is an atom with an unstable nucleus, which is a nucleus characterized by excess energy available to be imparted either to a newly created radiation particle within the nucleus or to an atomic electron. Radionuclide generators contain a parent isotope that decays to produce a radioisotope. The parent is usually produced in a nuclear reactor.
Radionuclide generator having first and second atoms of a first element

FIELD OF THE INVENTION

The invention is in the field of a radionuclide generator.

BACKGROUND OF THE INVENTION

A radionuclide is an atom with an unstable nucleus, which is a nucleus characterized by excess energy available to be imparted either to a newly created radiation particle within the nucleus or to an atomic electron. The radionuclide, in this process, undergoes radioactive decay, and emits one or more of the following: photons, negatron, positron, or alpha particles, directly or indirectly. These particles constitute ionizing radiation. Radionuclides occur naturally, and can also be artificially produced.

The number of radionuclides is uncertain. Some nuclides are stable and some decay. The decay is characterized by a half-life. Including artificially produced nuclides, more than 3300 nuclides are known (including ~3000 radionuclides), including many more (> ~2400) that have decay half-lives shorter than 60 minutes. This list expands as new radionuclides with very short half-lives are identified.

Radionuclides are often referred to by chemists and physicists as radioactive isotopes or radioisotopes. Radioisotopes with suitable half-lives play an important part in a number of constructive technologies (for example, nuclear medicine).

Radionuclide generators are devices in which a (daughter) radionuclide is generated from its parent precursor radionuclide and is optionally separated therefrom. The parent is usually produced in a nuclear reactor, which is a complex and expensive system. A typical example is the technetium-99m generator used in nuclear medicine. The parent produced in the reactor is molybdenum-99.

US 4,782,231 recites a standard component 99mTC elution generator useful for medical purposes. The invention further provides for efficient generation of 99mTC radionuclides from medium neutron flux irradiation of molybdenum in a natural
isotopic mixture.

The generator of US 4,782,231 and similar generators are not relevant to the present invention. US 4,782,231 recites standard chemical separation of two radionuclides of chemically different elements.

Radionuclides are used in two major ways: for their chemical properties and as sources of radiation. Radionuclides of familiar elements such as carbon can serve as tracers because they are assumed to be chemically identical to the non-radioactive nuclides, so almost all chemical, biological, and ecological processes treat them in the same way.

In nuclear medicine, radioisotopes are used for diagnosis, treatment, and research. Radioactive tracers emitting gamma rays or positrons can provide diagnostic information about a person’s internal anatomy and the functioning of specific organs. This is used in some forms of tomography: single-photon emission computed tomography (SPECT) and positron emission tomography (PET) scanning.

Radioisotopes are also a method of treatment in hematopoietic forms of tumors; the success for treatment of solid tumors has been limited. More powerful gamma sources sterilize syringes and other medical equipment.

Other uses are e.g. in biochemistry, genetics, and food preservation.

In gamma de-excitation, a nucleus gives off excess energy, by emitting a gamma ray. The element is not changed to another element in the process (no nuclear transmutation is involved).

Various examples of use of radionuclides exist.

For instance, according to current practice, $^{177}$Lu (half-life 6.7 d) is produced by a neutron activation of stable $^{176}$Yb containing targets according to the nuclear reaction $^{176}$Yb $(n,\gamma)^{177}$Yb $(\beta^-)^{177}$Lu. Subsequently, the $^{177}$Lu is chemically separated from the target $^{176}$Yb and parent radionuclide $^{177}$Yb, and a no-carrier added product of high specific activity is obtained. This approach exists next to a previously employed production route wherein activation of stable $^{176}$Lu containing targets takes place, which result by the nuclear reaction $^{176}$Lu $(n,\gamma)^{177}$Lu$^{177m}$Lu in a mixture of the radionuclides $^{177}$Lu and $^{177m}$Lu.

The presence of the long-lived (161 d) radionuclide $^{177m}$Lu -
which production can not be prevented - is a strong drawback of this approach for application in nuclear medicine; moreover, the presence of \(^{176}\text{Lu}\) atoms of the target material result in a lower specific radioactivity.

In order to emphasize relevance of provision of radionuclides, currently 500 patients per year are treated in Erasmus Medical Centre (EMC) in The Netherlands alone. The EMC purchases 2 batches of 1 Ci \(^{177}\text{Lu}\) per week.

Some problems with state of the art processes relate amongst others to:

a) Availability of \(^{177}\text{Lu}\) 'on demand' of a medical centre is limited. Therefore there is a need for regular purchase of new amounts of \(^{177}\text{Lu}\). The supply however may be interrupted, e.g. due to break-down of a supplier facility.

b) Production of no-carrier added \(^{177}\text{Lu}\) without the need of irradiating isotopically enriched \(^{176}\text{Yb}\) and associated chemical separations is not possible.

Medical centers depend e.g. on application of \(^{177}\text{Lu}\)-PRRT (peptide receptor radiation therapy) on the market availability and operationally of nuclear production reactors. It is noted that recently, research reactors have broken down unexpectedly, and that reactors have scheduled maintenance times as well.

Up till now, Medical centers have to regularly purchase new amounts of \(^{177}\text{Lu}\) and depend in this on the availability at the market and reactor schedules and -operation.

c) Irradiation of isotopically enriched \(^{176}\text{Yb}\) and chemical separations, is not done 'on demand' of a specific medical centre.

Disadvantages mentioned for specific examples such as \(^{177}\text{Lu}\) are in principle also applicable to other radionuclides or isotopes.

The present invention therefore relates to a method of providing a radionuclide generator, the generator, products comprising said generator, and use thereof, which overcomes one or more of the above disadvantages, without jeopardizing functionality and advantages.

SUMMARY OF THE INVENTION

The present invention relates in a first aspect to a method for production of a long-lived radioisotope generator
capable of yielding high specific, and/or carrier-free, radioactivity according to claim 1, a long-lived radioisotope generator, a product comprising said radioisotope generator, a single amount, a kit, and use thereof.

The present invention is particularly suited for production of a $^{177m}$Lu-$^{177}$Lu generator, as well as production of $^{44m}$Sc, $^{127m}$Te, $^{129m}$Te, $^{137m}$Ce, and $^{186m}$Re. The examples below also specifically relate to the aforementioned. It is noted that in principle the example of the $^{177m}$Lu-$^{177}$Lu generator is equally well applicable to other examples mentioned, and by no means limited to the $^{177m}$Lu-$^{177}$Lu example.

The present invention solves one or more of the above mentioned problems. The risk of lack of market availability and operational disruption of nuclear reactors is limited to a large extent; the present invention provides for on demand delivery of radio isotopes in a required amount for a significant longer period of time. In the case of Lu the period is extended from a multiple of 6.7 days (the half-life of $^{177}$Lu) to a multiple of 160 days (the half-life of $^{177m}$Lu), in other words an increase by a factor of about 25. A similar improvement is obtained for other atoms, specifically the ones mentioned above.

Further the need for a carrier is reduced or absent.

Therefore the present invention provides a generator with high specific activity. The specific activity is significantly increased, typically by at least a factor of 10, compared to chemically identical atoms, such as in an example $^{177m}$Lu and $^{176}$Lu where the increase factor is at least 100.

As indicated above the present invention provides a long-lived radioisotope generator. Long-lived is relative to the half-life of a daughter nuclide. The increase in generator life time is typically at least a factor 2, i.e. being useful two times longer, although a factor of more than 1000 is also achievable.

The present invention provides for production of high specific activity no-carrier added isotopes, such as $^{177}$Lu, without a need of irradiating an isotopically enriched target, such as $^{176}$Yb, and depending on the isotope without a need of associated chemical separations thereof. The present invention is therefore amongst others easier, e.g. in terms of process steps, and as a consequence is available on-demand, contrary to
most prior art isotopes, which have to be purchased.

It is noted that the invention relates to a generator comprising first and second radionuclides of the same chemical element: isotopes of the same chemical element have in principle the same chemical behavior and therefore can not normally be separated by conventional chemical methods; in an aspect, the invention provides separation.

The present invention provides medical centers with an easy option to apply the present isotopes, such as $^{177}$Lu-PRRT, largely without being dependent on e.g. the market availability and operational schedule of nuclear reactors.

The present invention provides continuous production of a, in an example $^{177m}$Lu-$^{177}$Lu, radionuclide generator of in the example $^{177}$Lu (half-life 6.7 d) from a parent (in the example $^{177m}$Lu (half-life 160 d)) during a prolonged period, in the example at least half a year after availability of the generator. Moreover, an eluted radio isotope, e.g. $^{177}$Lu, is no-carrier added.

Prior art techniques provide availability of an once-only amount of a radioisotope, such as $^{177}$Lu, from e.g. a neutron irradiated amount of in the example $^{176}$Lu or $^{176}$Yb, whereas the present invention enables e.g. a $^{177m}$Lu-$^{177}$Lu generator in which at desired intervals, amounts of daughter radioisotope e.g. $^{177}$Lu can be removed from a given amount of parent isotope e.g. $^{177m}$Lu.

Specifically the present generator provides in an example no-carrier added isotopes, having high specific activity. Such is required for various applications.

Under suited experimental conditions, the present radionuclide generator results in an assured availability of radionuclides of high specific radioactivity for an extended period of time e.g. dependent on the half-life of the parent radionuclide instead of the half-life of the daughter radionuclide.

Further, there are no disadvantages of the present process apart from the necessary entrance to a neutron source coupled to a radiochemical infrastructure.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates in a first aspect to
a method for production of a long-lived radioisotope, optionally incorporated into a generator, and capable of yielding no carrier added high specific activity according to claim 1.

In an example of the present method activating is performed by one or more of the following methods: neutron reaction, such as by bombarding by neutrons, proton reaction, photonuclear reactions, such as gamma- or X-ray, alpha particle reaction, and ion beam reaction.

It is noted that various routes starting from a target may lead to the present invention in that first and second atoms of a single element according to the invention are obtained. Typically activating is performed in well protected environments, thereby reducing a risk of contamination of the environment with radioisotopes, such as in nuclear reactors. In the present invention there is some preference for using smaller particles, such as indicated above, such as neutrons and protons.

In an example the bombardment of the target compound with neutrons occurs in a reactor, whereas according to another example the bombardment occurs outside the reactor in a neutron beam or in a proton beam from e.g. a cyclotron.

In an example of the present method target atoms, such as naturally occurring or isotopically enriched atoms, and method of production, are selected from the group comprising

- $^{176}$Lu atoms, $^{58}$Co atoms, $^{80}$Br atoms, $^{187}$Re atoms, $^{232}$Th atoms, and $^{198}$Hg atoms.

The following are examples of production routes for the first (parent) atoms listed:

- $^{44m}$Sc: $^{45}$Sc(2,2n)$^{44m}$Sc and $^{44}$Ca(p,n)$^{44m}$Sc
- $^{80m}$Br: $^{79}$Br(n,$\gamma$)$^{80m}$Br, $^{81}$Br(n,2n)$^{80m}$Br and $^{80}$Se(p,n)$^{80m}$Br
- $^{121m}$Sn: $^{120}$Sn(n,$\gamma$)$^{121m}$Sn, $^{122}$Sn(n,2n)$^{121m}$Sn, $^{121}$Sb(n,p)$^{121m}$Sn and $^{235}$U(n,f)$^{121m}$Sn
- $^{121m}$Te: $^{120}$Te(n,$\gamma$)$^{121m}$Te, $^{122}$Te(n,2n)$^{121m}$Te and $^{121}$Sb(p,n)$^{121m}$Te
- $^{127m}$Te: $^{126}$Te(n,$\gamma$)$^{127m}$Te, $^{128}$Te(n,2n)$^{127m}$Te, $^{127}$I(n,p)$^{127m}$Sn and $^{235}$U(n,f)$^{127m}$Te
- $^{129m}$Te: $^{128}$Te(n,$\gamma$)$^{129m}$Te, $^{130}$Te(n,2n)$^{129m}$Te, $^{132}$Xe(n,$\alpha$)$^{129m}$Te and $^{235}$U(n,f)$^{129m}$Te
- $^{137m}$Ce: $^{136}$Ce(n,$\gamma$)$^{137m}$Ce, $^{138}$Ce(n,2n)$^{137m}$Ce, $^{138}$La(p,2n)$^{137m}$Ce and $^{139}$La(p,3n)$^{137m}$Ce
- $^{177m}$Lu: $^{176}$Lu(n,$\gamma$)$^{177m}$Lu and $^{177}$Hf(p)$^{177m}$Lu
\[ 186^{m}\text{Re}: 185^{m}\text{Re}(n,\gamma)186^{m}\text{Re}, \quad 187^{m}\text{Re}(n,2n)186^{m}\text{Re}, \quad 186^{m}\text{W}(p,n)186^{m}\text{Re} \]

\[ 186^{m}\text{Os}(n,p)186^{m}\text{Re} \]

\[ 192^{m}\text{Ir}: 191^{m}\text{Ir}(n,\gamma)192^{m}\text{Ir}, \quad 193^{m}\text{Ir}(n,2n)192^{m}\text{Ir}, \quad 192^{m}\text{Os}(p,n)192^{m}\text{Ir} \]

\[ 192^{m}\text{Pt}(n,p)192^{m}\text{Ir} \]

\[ 198^{m}\text{Au}: 197^{m}\text{Au}(n,\gamma)198^{m}\text{Au}, \quad 198^{m}\text{Pt}(p,n)198^{m}\text{Au} \quad \text{and} \quad 198^{m}\text{Hg}(n,p)198^{m}\text{Au} \]

\[ 242^{m}\text{Am}: 241^{m}\text{Am}(n,\gamma)242^{m}\text{Am}. \]

It is therefore noted that various routes starting from a target may lead to the present invention in that first and second atoms of a single element according to the invention are obtained.

In an example of the present method first atoms are selected from the group comprised of; 44\text{m} Sc atoms, 80\text{m} Br atoms, 121\text{m} Sn atoms, 121\text{m} Te atoms, 127\text{m} Te atoms, 129\text{m} Te atoms, 137\text{m} Ce atoms, 177\text{m} Lu atoms, 186\text{m} Re atoms, 192\text{m} Ir atoms, 198\text{m} Au atoms, and 242\text{m} Am atoms, preferably 177\text{m} Lu atoms, 44\text{m} Sc, 127\text{m} Te, 129\text{m} Te, 137\text{m} Ce, and 186\text{m} Re. The decay characteristics of these parent/daughter atoms are all experimentally found to be useful (e.g. in a medical / research sense).

In an example of the present method second atoms are selected in accordance with first atoms from the group comprised of; 44\text{m} Sc atoms, 80\text{m} Br atoms, 121\text{m} Sn atoms, 121\text{m} Te atoms, 127\text{m} Te atoms, 129\text{m} Te atoms, 137\text{m} Ce atoms, 177\text{m} Lu atoms, 186\text{m} Re atoms, 192\text{m} Ir atoms, 198\text{m} Au atoms, and 242\text{m} Am atoms, such as 177\text{m} Lu atoms.

It is noted that the following improvements in terms of increased life (long lived) are obtained. For 44\text{m} Sc atoms the half-life is about 15 times longer than for 44\text{m} Sc atoms. For 80\text{m} Br atoms the half-life is about 15 times longer than for 80\text{m} Br atoms. For 121\text{m} Sn atoms the half-life is about 17800 times longer than for 121\text{m} Sn atoms. For 121\text{m} Te atoms half-life is about 9 times longer than for 121\text{m} Te atoms. For 127\text{m} Te atoms the half-life is about 280 times longer than for 127\text{m} Te atoms. For 129\text{m} Te atoms half-life is about 695 times longer than for 129\text{m} Te atoms. For 137\text{m} Ce atoms the half-life is about 4 times longer than for 137\text{m} Ce atoms. For 177\text{m} Lu atoms the half-life is about 25 times longer than for 177\text{m} Lu atoms. For 186\text{m} Re atoms the half-life is about 2\times10^7 times longer than for 186\text{m} Re atoms. For 192\text{m} Ir atoms the half-life is about 1100 times longer than for 192\text{m} Ir atoms. For 198\text{m} Au atoms the half-life is about 0.8 times longer than for 198\text{m} Au atoms. For 242\text{m} Am atoms the half-life is about 7.7\times10^4 times longer than for 242\text{m} Am atoms.
In an example the present method further comprises a step of separating the first atoms under formation of second atoms, preferably by chemical separation.

The separation is obtained according to the invention by taking advantage of the emission of a highly converted gamma-ray in the decay of parent atoms. It is believed that this emission results in an Auger cascade in which the orbital electrons are ejected from their shells. Consequently, a variety of highly positively charged daughter atoms are formed. The Coulomb repulsion between these atomic fragments may, in the case of a chemical compound, result in the rupturing of chemical bonds between compound and daughter atoms, and as a consequence these daughter atoms will be separated from both the target compound and the parent radionuclide. In a further example a similar mechanism may occur when target, parent and daughter atoms are present as a solid, e.g. a solid layer. The present invention results in a specific radioactivity of daughter which is typically at least a factor of 100 higher than if the daughter is not separated from the target.

Accordingly the present invention relates to a process for the production of no-carrier added daughter atoms, such as $^{177}\text{Lu}$ atoms, of high specific radioactivity, characterized in that atoms, such as $^{176}\text{Lu}$ atoms, are bombarded with neutrons resulting in formation of radioactive atoms, such as $^{177m}\text{Lu}$ (half-life 160 d), and radioactive $^{177}\text{Lu}$ (half-life 6.7 d); the latter formed by direct production from $^{176}\text{Lu}$ as well as a decay product of $^{177m}\text{Lu}$), all incorporated in the target. The radioactive $^{177}\text{Lu}$ atoms separate by bond rupture from the $^{176}\text{Lu}$ and $^{177m}\text{Lu}$ atoms contained in the target.

In an example, the radionuclide generator comprises the following; the neutron activated $^{176}\text{Lu}$ plus its reaction products, $^{177m}\text{Lu}$ and $^{177}\text{Lu}$ to e.g. a solution. The solution is mixed with another solvent to which only the $^{177}\text{Lu}$ is transferred from the mixture of radioisotopes. Similar examples are envisaged for the other examples mentioned.

In an example a generator, such as a $^{177m}\text{Lu}\text{-}^{177}\text{Lu}$ generator, is provided loaded with 0.02-500 Ci radio isotope, such as from 0.5-250 Ci, such as from 1-100 Ci, such as 2-50 Ci, such as with $^{177m}\text{Lu}$. Such a generator can in an example provide 7-8 batches of radio isotope, such as $^{177}\text{Lu}$, with activities
varying from 175 - 0.001 Ci during a period of 7-8 months. For a weekly consumption as described above, the EMC would need 2-4 177mLu-177Lu generators (procured sequentially over 2-4 weeks) for having a continuous weekly availability of 177Lu during a period of 7-8 months rather than purchase 80 batches of 177Lu over the same period, which is a clear advantage.

The liquid used may be of an oxidizing nature and or have some ionic strength in order to facilitate the collection of the second (daughter) atoms. This liquid may be selected such that it can be used in chemical separation of second (daughter) atoms from any other chemical impurity. In the case of the 177Lu, this could be the removal of 177Hf.

This bond rupture continues also after completion of the irradiation, as soon as 177Lu is formed by the decay of 177mLu. The separated 177Lu radioactive atoms are removed from the said chemical compound or matrix by a chemical process with high selectivity for 177Lu compared to the chemically identical 175/176Lu atoms and parent radionuclide 177mLu. After this removal, new 177Lu atoms are formed from the decay of 177mLu, and the procedure of removal of 177Lu can be repeated after sufficient formation time. A 177mLu-177Lu radionuclide generator is thus created, allowing the regular removal of amounts of 177Lu from a single amount of 177mLu.

It is noted that isotopes of the same chemical element have the same chemical behavior and therefore can not normally be separated by conventional chemical methods.

In an example of the present method the second atoms are separated into a liquid medium, such as a gas, a liquid, and supercritical fluid, or a combination thereof.

The liquid medium should be capable of receiving daughter atoms. If used directly in a subsequent application, the liquid medium should be acceptable within that application as well, e.g. non-toxic, resembling body fluid, etc.

In an example of the present method, the liquid medium preferably is water and comprises one or more solutes, such as salts, acids, bases, adjuvants, saccharides, and stabilizers.

Such liquid medium may be adapted to mimic e.g. a body fluid, e.g. in terms of typical concentrations of solutes therein.
The present invention relates in a second aspect to a long-lived, high specific activity and/or carrier-free radioisotope generator according to claim 98.

It is noted that dimensions of the generator can be adapted, e.g. increasing or decreasing a size thereof, thereby potentially controlling the amount of radioisotope being released. In this respect also the amount of liquid provided to the generator, surface of the generator, etc., can be adapted.

The present invention relates in a third aspect to a product comprising the long-lived, high specific activity and/or carrier-free radioisotope generator according to the invention.

In an example of the present product the radioisotope generator:

- is present on a surface, and/or
- is present in a liquid, and/or
- is present in a matrix, and/or
- is present in a chemical compound, and/or
- is present in a complex, and/or combinations thereof.

In an example the generator is present having a large surface area and a small volume, e.g. as a layer of 1 atom thick (~100 pm) -10 μm, such as 1 nm -2 μm. Thereby release of daughter atoms is improved.

As such as supporting layer/structure may be provided, such as a chemically inert layer, a zeolite, etc. Even further the generator may be present in a compound, such as a chemical compound capable of forming (chemical) bonds with the daughter and parent atoms, and optionally with the target atoms, or likewise in a complex. The generator may also be present in a liquid, such as water, a gas, such as nitrogen, and the like.

In an example of the present product the radioisotope generator is present on a chemically inert surface, such as an inner surface of a tube like structure, a surface of a particle, is present dissolved in a liquid, is present in a 3D- and/or 2D-matrix, such as a zeolite, is in a chemical compound, such as in an organometallic compound, is in a complex, such as in a complex with one or more organic molecules, in a complex with one or more inorganic molecules, and combinations thereof.

In an example of the present product it comprises
a tube, the tube comprising an inner surface, being formed of a chemically inert material, such as glass, Teflon, a suitable polymer, silicon, a metal such as copper, tantalum, titanium, metal alloy, or a combination thereof,

an inlet for providing a liquid into the tube,

an outlet for releasing the liquid from the tube,

a protection surrounding the tube for preventing radiation from effecting the environment, such as a lead comprising protection, and

a long-lived, high specific activity or carrier-free radioisotope generator inside the tube.

Through the inlet typically a liquid is provided to the generator. The liquid collects the daughter radionuclide.

After collecting a sufficient amount of radioisotope the liquid is released through the outlet. The amount released per unit time can be calculated, e.g. in order to determine residence time. Similar, a continuous flow of liquid may be provided, typically at a low flow rate, providing liquid comprising the daughter radionuclide. The flow rate may be from 0.1 ml/h-50 ml/h. Therewith a controllable amount of radioisotope can be provided.

The present invention relates in a fourth aspect to a single amount of radioactive atoms, such as $^{177}$Lu atoms, obtainable by a method according to the invention, or provided by a product according to the invention or generator according to the invention. The single amount is from 0.02-5 Ci, such as from 0.02-1.6 Ci, such as from 0.1-1.0 Ci.

The present invention relates in a fifth aspect to a kit comprising a product according to the invention and/or a single amount according to the invention.

In an example the kit comprises the above generator. Further the kit may comprise a liquid, such as 0.1 - 1000 mL per single amount to be obtained. Preferably the liquid comprises further components, such as the above solutes. As such the obtained single amount may be directly used for its intended (final) purpose. The kit may further comprise a syringe, such as a 10-250 ml syringe. Typically also gloves are supplied. The kit may further comprise a storage kit. In an example the kit is substantially free of microorganisms.

The present invention relates in a sixth aspect to
a use of a product according to the invention and/or a single amount according to the invention for the preparation of a medicament, such as for use in therapy, such as peptide receptor radiation therapy.

The invention is further detailed by the accompanying figures, which are exemplary and explanatory of nature and are not limiting the scope of the invention. To the person skilled in the art it may be clear that many variants, being obvious or not, may be conceivable falling within the scope of protection, defined by the present claims.

FIGURES

The invention although described in detailed explanatory context may be best understood in conjunction with the accompanying figures.

Figure 1-2 show a schematic representation of an example of a generator (such as the product of the claims).

DETAILED DESCRIPTION OF THE DRAWINGS / FIGURES

Figure 1 shows a schematic representation of a generator. Therein a tube (1) is shown, the tube comprising an inner surface, being formed of a chemically inert material, such as glass, Teflon, a suitable polymer, silicon, a metal such as copper, tantalum, titanium, metal alloy, or a combination thereof. Further an inlet (2) is shown for providing a liquid into the tube. A typical inner dimension of the inlet is .01-10 mm, such as 0.3-5 mm. Also the inlet is of a chemically inert material. Possibly it may also comprise a protection layer. Further an outlet (3) is shown for releasing the liquid from the tube. The outlet and inlet typically have similar properties. In order to protect the environment from radiation optionally a protection (6) surrounding the tube is present, such as a lead comprising protection. The product further comprises a long-lived, high specific activity or carrier-free radioisotope generator inside the tube. The generator can be in any suitable form, such as described above.

Figure 2 shows details of a generator.

In Figure 2a a section of a plated tube is shown comprising element A: a deposited layer of first atoms (monoatomic or multiple layers); the layer may include non-
radioactive atoms of the same element); element B: a chemically inert surface (e.g. glass, tantalum, silicon, etc.), and element C: a structural material; this material may include a shielding material (e.g. lead).

In figure 2b a further example is given, wherein the deposited layer comprises spherical particles or the like, typically particles having a diameter of 0.2-10 nm.

In figure 2c the generator is filled with plated beads, having a similar composition as above.

It should be appreciated that for commercial application it may be preferable to use one or more variations of the present system, which would similar be to the ones disclosed in the present application and are within the spirit of the invention.
1. Method for production of a long-lived radioisotope generator capable of yielding high specific, and/or carrier-free, radioactivity, comprising the steps of:

(a) providing a target,

(b) activating the target thereby obtaining a radioisotope generator, the radioisotope generator comprising

(i) radioactive first atoms (parent) of a first element having a first half-life, the first atoms being in a metastable state,

(ii) second atoms (daughter) of a first element being radioactive having a second half-life, the second atoms being in a second state, such as the ground state, wherein the second atom is a radioactive daughter of the first parent atom, which radioactive daughter is formed by emission of a highly converted gamma-ray transition, such as by E2, E3, E4, E5, M2, M3, M4, M5, or combination thereof, and wherein optionally the first half-life is at least 2 times longer than the second half-life, preferably at least 5 times longer, even more preferably at least 10 times longer, such as at least 25 times longer, and

(c) optionally incorporating the activated target, including first atoms, second atoms, and inactive target atoms, by electrochemical or physical deposition onto an inert surface.

2. Method according to claim 1, wherein activating is performed by one or more of the following methods: neutron reaction, proton reaction, photonuclear reactions, such as gamma- or X-ray, alpha particle reaction, and ion beam reaction.

3. Method according to claims 1 or 2, wherein target atoms, such as naturally occurring or isotopically enriched atoms, and method of production, are selected from the group comprising $^{176}$Lu atoms, $^{56}$Co atoms, $^{80}$Br atoms, $^{187}$Re atoms, $^{232}$Th atoms, and $^{198}$Hg atoms.
4. Method according to any of the preceding claims, wherein first atoms are selected from the group comprised of: $^{44m}$Sc atoms, $^{80m}$Br atoms, $^{121m}$Sn atoms, $^{121m}$Te atoms, $^{127m}$Te atoms, $^{129m}$Te atoms, $^{137m}$Ce atoms, $^{177m}$Lu atoms, $^{186m}$Re atoms, $^{192m}$Ir atoms, $^{198m}$Au atoms, and $^{242m}$Am atoms, preferably $^{177m}$Lu, $^{44m}$Sc, $^{127m}$Te, $^{129m}$Te, $^{137m}$Ce, and $^{186m}$Re atoms.

5. Method according to any of the preceding claims, wherein second atoms are selected in accordance with first atoms from the group comprised of: $^{44}$Sc atoms, $^{80}$Br atoms, $^{121}$Sn atoms, $^{121}$Te atoms, $^{127}$Te atoms, $^{129}$Te atoms, $^{137}$Ce atoms, $^{177}$Lu atoms, $^{186}$Re atoms, $^{192}$Ir atoms, $^{198}$Au atoms, and $^{242}$Am atoms, preferably $^{177}$Lu atoms.

6. Method according to any of the preceding claims, further comprising a step of: separating the first atoms under formation of second atoms, preferably by chemical separation, preferably wherein the second atoms are separated into a liquid medium, such as a gas, a liquid, and supercritical fluid, or a combination thereof.

7. Method according to claim 6, wherein the liquid medium preferably is water and comprises one or more solutes, such as salts, acids, bases, adjuvants, saccharides, and stabilizers.

8. Long-lived, high specific activity and/or carrier-free radioisotope generator, the radioisotope generator comprising

(i) radioactive first atoms (parent) of a first element having a first half-life, the first atoms being in a metastable state,

(ii) second atoms (daughter) of the first element being radioactive having a second half-life, the second atoms being in a second state, such as the ground state, wherein the second atom is a radioactive daughter of the first atom (parent), and the radioactive daughter is formed by emission of a highly converted gamma-ray, such as by E2, E3, E4, E5, M2, M3, M4, M5, or combination thereof, and wherein optionally the first half-life is at least 2 times longer than the second half-life, preferably at least 5 times longer, even more preferably at least 10 times longer, such as at least 25 times longer, obtainable by a method ac-
cording to any of claims 1-7.

9. Product comprising the long-lived, high specific activity and/or carrier-free, radioisotope generator according to claim 8.

10. Product according to claim 9, wherein the radioisotope generator:

is present on a surface, and/or
is present in a liquid, and/or
is present in a matrix, and/or
is present in a chemical compound, and/or
is present in a complex, and/or combinations thereof.

11. Product according to claim 10, wherein the radioisotope generator is present on a chemically inert surface, such as an inner surface of a tube like structure, a surface of a particle, is present dissolved in a liquid, is present in a 3D- and/or 2D-matrix, such as a zeolite, is in a chemical compound, such as in an organometallic compound, is in a complex, such as in a complex with one or more organic molecules, in a complex with one or more inorganic molecules, and combinations thereof.

12. Product according to claim 11, comprising a tube (1), the tube comprising an inner surface, being formed of a chemically inert material, such as glass, Teflon, a suitable polymer, silicon, a metal such as copper, tantalum, titanium, metal alloy, or a combination thereof, an inlet (2) for providing a liquid into the tube, an outlet (3) for releasing the liquid from the tube, optionally a protection (6) surrounding the tube for preventing radiation from effecting the environment, such as a lead comprising protection, and

a long-lived, high specific activity or carrier-free radioisotope generator inside the tube.

13. Single amount of radioactive atoms, such as $^{177}$Lu atoms, obtainable by a method according to any of claims 1-7, or provided by a product according to any of claims 9-12 or generator according to claim 8.
14. Kit comprising a product according to any of claims 10-13 and/or a single amount according to claim 13.

15. Product according to any of claims 9-12 and/or a single amount according to claim 13 for the preparation of a medicament, such as for use in radiotherapy or imaging, such as peptide receptor radiation therapy, for the purpose of diagnosis or treatment.
A. CLASSIFICATION OF SUBJECT MATTER

INV. G21G1/00
ADD.

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)

G21G

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

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

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>X</td>
<td>US 4 782 231 A (SVOBODA KRISTIAN [CS] ET AL) 1 November 1988 (1988-11-01) cited in the application abstract; claims; figures</td>
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"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

11 March 2013

Date of mailing of the international search report

19/03/2013

Name and mailing address of the ISA/European Patent Office, P.B. 5016 Patentlaan 2, NL - 2280 HV Rijswijk, Tel. (+31-70) 340-2040, Fax. (+31-70) 340-3016

Authorized officer

Smith, Christopher
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