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(57) Abstract: The radiopharmaceutical ^{177}Lu-PSMA I&T including optically enriched mixtures thereof are provided, including in high purities with extended shelf life in the absence of undesired impurities. Further provided are methods of synthesis of ^{177}Lu-PSMA I&T including optically enriched mixtures thereof under comparatively reduced reaction times and/or temperatures, and pharmaceutical compositions and methods of treatment that comprise ^{177}Lu-PSMA I&T.

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RADIOPHARMACEUTICAL AND METHODS

This application claims the benefit of U.S. provisional application number 63/051,335 filed July 13, 2020, and U.S. provisional application number 63/143,664 filed January 29, 2021, both of which applications are incorporated by reference herein in their entirety.

Field

The radiopharmaceutical lutetium ^{177}Lu-PSMA I&T including optically enriched mixtures thereof are provided, including in high purities with extended shelf life. Further provided are methods of synthesis of ^{177}Lu-PSMA I&T including optically enriched mixtures thereof and pharmaceutical compositions that comprise ^{177}Lu-PSMA I&T including optically enriched mixtures thereof.

Background

Radiopharmaceuticals have been used for a variety of therapeutic and diagnostic indications. Among others, radiolabeled molecules have been useful to treat various malignant tumors.

Use of these pharmaceutical agents presents certain challenges, including with respect to the formation of the active pharmaceutical ingredient by combination of a radionuclide with a targeting agent whereby the resulting active pharmaceutical ingredient has low purity. Furthermore, the subsequent formulation of the active pharmaceutical ingredient to form a pharmaceutical agent has poor stability and decreased shelf-life. In particular, therapeutic compositions comprising a radionuclide may undergo radiolysis during any one or more of formation of the active pharmaceutical ingredient, preparation of the pharmaceutical agent and storage of a pharmaceutical composition. During radiolysis, radionuclide emissions may react with other groups of the active pharmaceutical ingredient thereby resulting in decomposition of the active pharmaceutical

ingredient and a reduction in purity which limits the shelf-life and clinical usefulness of the pharmaceutical composition.

It thus would be desirable to have new pharmaceutical agents. It would be particularly desirable to have such agents that exhibit improved purities, stability and shelf-lives.

SUMMARY

We now provide, *inter alia*, ^{177}Lu-PSMA I&T having high purity, methods of preparing the compound, and pharmaceutical compositions and methods of treatment comprising ^{177}Lu-PSMA I&T.

More particularly, we now provide ^{177}Lu-PSMA I&T in high purities including for extended storage times. We also provide ^{177}Lu-PSMA I&T in the absence of undesired impurities.

We also have found methods for producing ^{177}Lu-PSMA I&T under comparatively reduced reaction times and/or temperatures. We also have found that such methods can produce ^{177}Lu-PSMA I&T in enhanced purities.

Still further, we have found additional methods for producing high purity ^{177}Lu-PSMA I&T, including by at least substantially or completely excluding gentisate compounds from the reaction to form ^{177}Lu-PSMA I&T.

Still further, we have found that gentisate compounds can form adducts with ^{177}Lu-PSMA I&T during the formation of ^{177}Lu-PSMA I&T.

We have also surprisingly found that addition of one or more ascorbate compounds to the formed ^{177}Lu-PSMA I&T can significantly enhance shelf life of the ^{177}Lu-PSMA I&T, including maintaining high radiochemical purity over extended storage times. We have also surprisingly found that addition of one or more gentisate compounds to the formed ^{177}Lu-PSMA I&T can significantly enhance shelf life of the ^{177}Lu-PSMA I&T,

including maintaining high radiochemical purity over extended storage times without forming impurities, including gentisate adduct impurities.

In certain aspects, optically enriched mixtures of ^{177}Lu-PSMA I&T are provided.

^{177}Lu-PSMA I&T is a complex of lutetium (^{177}Lu) and EuK-Sub-kf-iodo-y-DOTAGA. The term "complex" herein generally refers to a union of ^{177}Lu and the ligand EuK-Sub-kf-iodo-y-DOTAGA inclusive of chemical and physical variations that may exist with the joined or associated lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA (designated as ^{177}Lu-PSMA I&T).

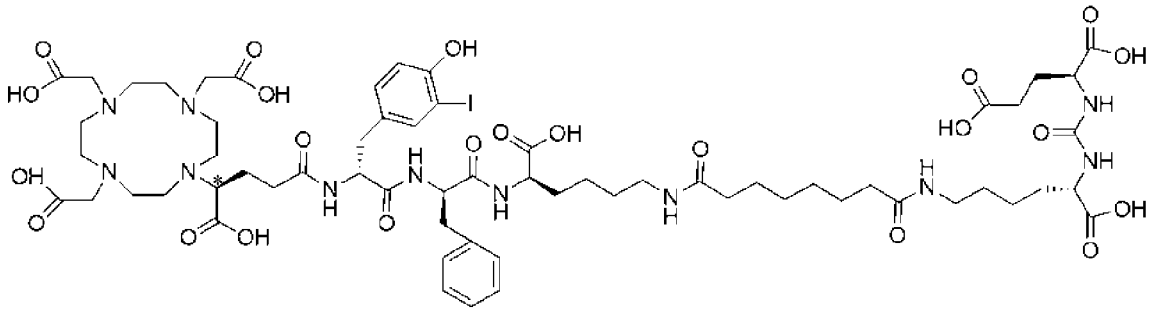
EuK-Sub-kf-iodo-y-DOTAGA and ^{177}Lu-PSMA I&T each has several possible stereoisomers, including the *R* and *S* isomers of the carbon that is an N-ring substituent of the tetraazacyclotetradecane moiety of those compounds. References herein to EuK-Sub-kf-iodo-y-DOTAGA and ^{177}Lu-PSMA I&T without further limitation includes all possible stereoisomers of each of those compounds and particularly both the noted *R* and *S* isomers.

In certain aspects, racemic mixtures of ^{177}Lu-PSMA I&T and EuK-Sub-kf-iodo-y-DOTAGA are provided, including for use in the present pharmaceutical compositions and methods.

In other preferred aspects, optically enriched mixtures of ^{177}Lu-PSMA I&T and EuK-Sub-kf-iodo-y-DOTAGA are provided, including for use in the present pharmaceutical compositions and methods.

In a preferred aspect, *S* isomer-enriched EuK-Sub-kf-iodo-y-DOTAGA is provided, i.e. EuK-Sub-kf-iodo-y-DOTAGA that is comprised of a weight excess of the *S* isomer

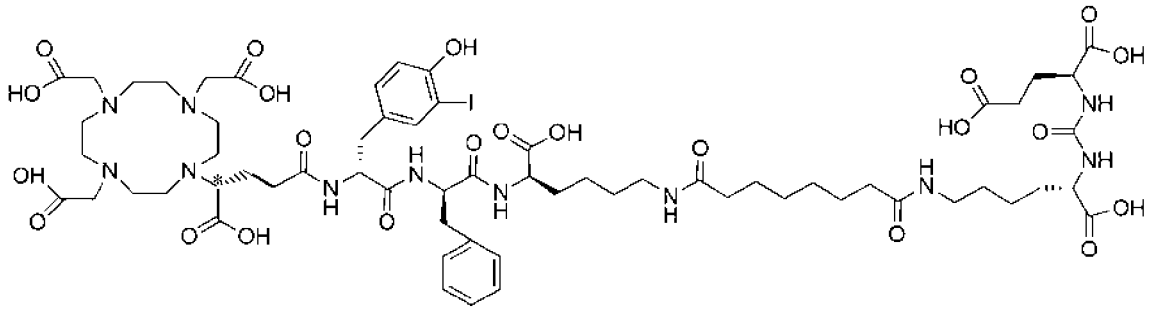
(referring to the *carbon having N-ring substitution) of the following structure 1A:



1A

In this aspect, generally preferred is EuK-Sub-kf-iodo-y-DOTAGA that is substantially optically enriched with the *S* isomer of structure 1A, or is an enantiomerically pure mixture of the *S* isomer of structure 1A.

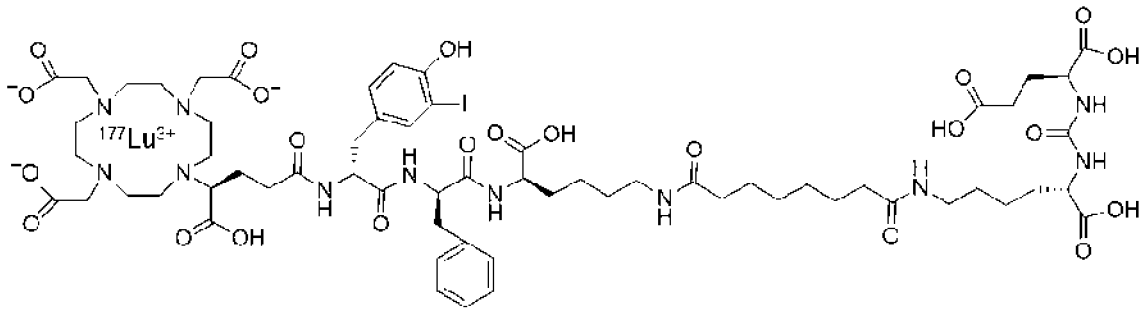
In another aspect, *R* isomer-enriched EuK-Sub-kf-iodo-y-DOTAGA is provided, i.e. EuK-Sub-kf-iodo-y-DOTAGA that is comprised of a weight excess of the *R* isomer (referring to the *carbon having N-ring substitution) of the following structure 1B:



1B

In such aspect, generally preferred is EuK-Sub-kf-iodo-y-DOTAGA that is substantially optically enriched with the *R* isomer of structure 1B, or is an enantiomerically pure mixture of the *R* isomer of structure 1B.

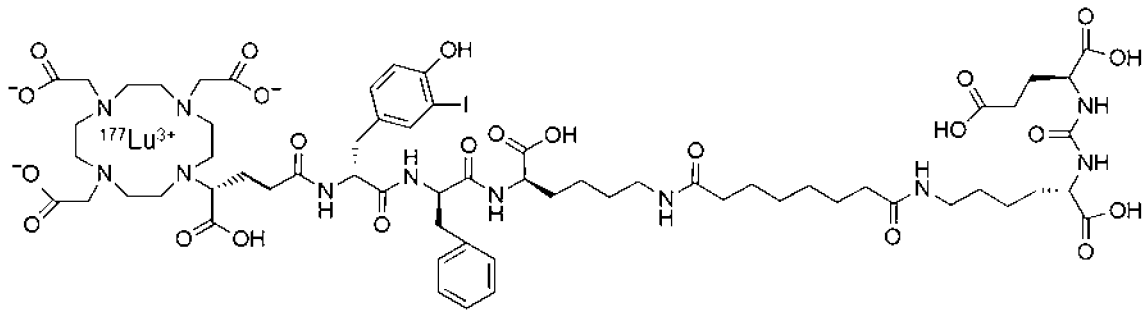
Additionally, in certain preferred aspects, the *R* of ^{177}Lu-PSMA I&T is provided, including for use in the present pharmaceutical compositions and methods. That *S* isomer may be represented by the following structure 2A:



2A

In this aspect, generally preferred is ^{177}Lu-PSMA I&T that is substantially optically enriched with the *S* isomer of structure 2A, or is an enantiomerically pure mixture of the *S* isomer of structure 2A.

In another aspect, the *R* isomer of ^{177}Lu-PSMA I&T is provided, including for use in the present pharmaceutical compositions and methods. That *R* isomer may be represented by the following structure 2B:



2B

In this aspect, generally preferred is ^{177}Lu-PSMA I&T that is substantially optically enriched with the *R* isomer of structure 2B, or is an enantiomerically pure mixture of the *R* isomer of structure 2B.

The present ^{177}Lu-PSMA I&T compound can exhibit particularly favorable chemical or radiochemical purities, including greater than 95, 96, 97, 98, 99, 99.5, 99.6,

99.7, 99.8 or 99.9 percent radiochemical purity and/or substantial absence of one or more prior impurities.

Thus, significantly, ^{177}Lu-PSMA I&T is now provided for the first time at the high purities as disclosed herein, including with the absence of prior impurities.

Additionally, new methods have been found to produce ^{177}Lu-PSMA I&T with high (e.g., > 99 or 99.5 molar percent) incorporation of lutetium-177. Surprisingly, the present methods can provide such high lutetium-177 incorporation under mild conditions, including reduced reaction times and/or reduced reaction temperatures.

More particularly, in one aspect, methods are provided for preparing ^{177}Lu-PSMA I&T that include admixing lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA in the complete or substantial absence of one or more gentisate compounds.

It has been found that at least substantial absence of any gentisate compounds during the incorporation reaction (including heating) can substantially reduce impurities that would otherwise be produced through lutetium-177 incorporation. That is, it has been found that exclusion of any gentisate compounds from the reaction to incorporate lutetium-177 with EuK-Sub-kf-iodo-y-DOTAGA can produce lutetium ^{177}Lu-PSMA I&T with reduced impurities. See, for instance, Examples 1 and 2 which follow.

Gentisate compounds would be substantially absent (or an admixture comprising lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA would be substantially free of gentisate compound(s)) if one or more gentisate compounds are present in an amount of less than 10, 8, 5, 4, 3, 2, 1 or 0.5 weight percent relative to the weight amount of one or more other stabilizer compounds (including ascorbate compounds) present during an incorporation reaction.

As referred to herein, “the incorporation reaction” or similar term refers to the reaction to incorporate (e.g. complex) lutetium-177 with EuK-Sub-kf-iodo-y-DOTAGA to thereby produce ^{177}Lu-PSMA I&T. In certain aspects, the incorporation reaction may

include admixing lutetium-177 with EuK-Sub-kf-iodo-y-DOTAGA and heating the lutetium-177/ EuK-Sub-kf-iodo-y-DOTAGA admixture.

Methods also are provided for preparing ^{177}Lu-PSMA I&T that include admixing lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA in the presence of one or more ascorbate compounds suitably in an aqueous composition. The one or more ascorbate compounds may be referred to as a component of the "Reaction Composition" or similar term when added to or otherwise present with either lutetium-177 or EuK-Sub-kf-iodo-y-DOTAGA as part of the reaction to incorporate (e.g. complex) lutetium-177 with EuK-Sub-kf-iodo-y-DOTAGA to prepare lutetium ^{177}Lu-PSMA I&T. The Reaction Composition is suitably an aqueous composition.

The Reaction Composition may comprise one or more other agents, particularly one or more distinct organic compounds in addition to ascorbate compound(s). Such additional distinct organic compounds sometimes are referred to herein as "stabilizer compounds." The term "stabilizer compound" or "stabilizer compounds" includes one or more ascorbate compounds.

In particular aspects, the EuK-Sub-kf-iodo-y-DOTAGA precursor (structure 1A and/or 1B) may be diluted before admixture with a lutetium-177 compound, such as diluting a compound of structure 1A and/or 1B with an aqueous composition preferably comprising one or more ascorbate compounds.

It has been found that the presence of one or more ascorbate compounds during the incorporation reaction (including heating) can substantially reduce impurities that would otherwise be produced through lutetium-177 incorporation.

In particular, it has been found that the presence of one or more ascorbate compounds during the incorporation reaction (including heating) can substantially reduce impurities that would otherwise be produced through lutetium-177 incorporation in the absence of a radioprotectant or in the presence of gentisic acid, for example where a gentisate adduct is formed with ^{177}Lu-PSMA I&T.

In preferred systems, one or more ascorbate compounds are present during the incorporation reaction (including heating) together with at least substantial absence or preferably complete absence of one or more gentisate compounds during that incorporation reaction to reduce impurities that would otherwise be produced through lutetium-177 incorporation. In such an aspect, gentisate compound(s) would be substantially absent (or an admixture comprising lutetium-177, EuK-Sub-kf-iodo-y-DOTAGA and one or more ascorbate compounds would be substantially free of gentisate compound(s)) if one or more gentisate compounds were present in an amount of less than 10, 8, 5, 4, 3, 2, 1 or 0.5 weight percent relative to the weight amount of one or more ascorbate compounds present during an incorporation reaction.

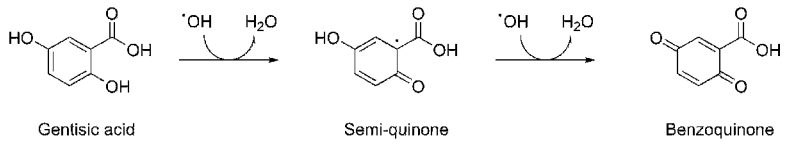
It has been found that a substantial or complete absence of one or more gentisate compounds during the incorporation reaction can reduce or avoid the occurrence or formation of an impurity that has been detected by high-performance liquid chromatography (HPLC).

The impurity or impurities that has been observed upon use of one or more gentisate compounds such as gentisic acid during the incorporation reaction to form ^{177}Lu-PSMA I&T is sometimes referred to herein as “gentisate adduct impurity”.

In one aspect, a “gentisate adduct impurity” as referred to herein has been characterized as have a retention time in the region of 10.2 minutes by high-performance liquid chromatography (HPLC) with a by high-performance liquid chromatography (HPLC) with a Waters XBridge BEH Phenyl-Hexyl Column, 130Å, 3.5 µm, 4.6 mm X 150 mm using 0.1% trifluoracetic acid in water (Mobile Phase A) and 0.1% trifluoracetic acid in acetonitrile. A linear gradient from 85% Mobile Phase A to 55% Mobile Phase A over 12 minutes is used and the ratio is held for 15 minutes. The absence of such impurity would be demonstrated by a no peaks (e.g. by visible review of spectra) being present in the 9 to 12 minute region of an HPLC chromatogram corresponding, in particular aspects the 9 or 9.5 to 10.5 or 11 minute region or the about 10.2 minute region as exemplified by the radio chromatograms of FIGS. 1C and 1D.

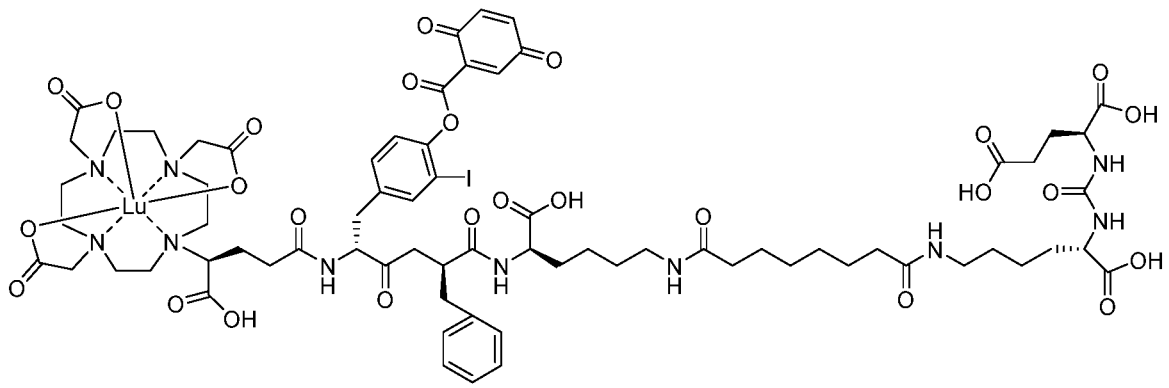
In another aspect, a "gentisate adduct impurity" as referred to herein may be characterized as a compound that include a covalent linkage of 1) a gentisate compound such as gentisic acid or reaction product or other derivative of such gentisate compound and 2) EuK-Sub-kf-iodo-y-DOTAGA.

For instance, without being bound by any theory, gentistic acid oxidation can result in formation of a benzoquinone as shown in the following Scheme 1.

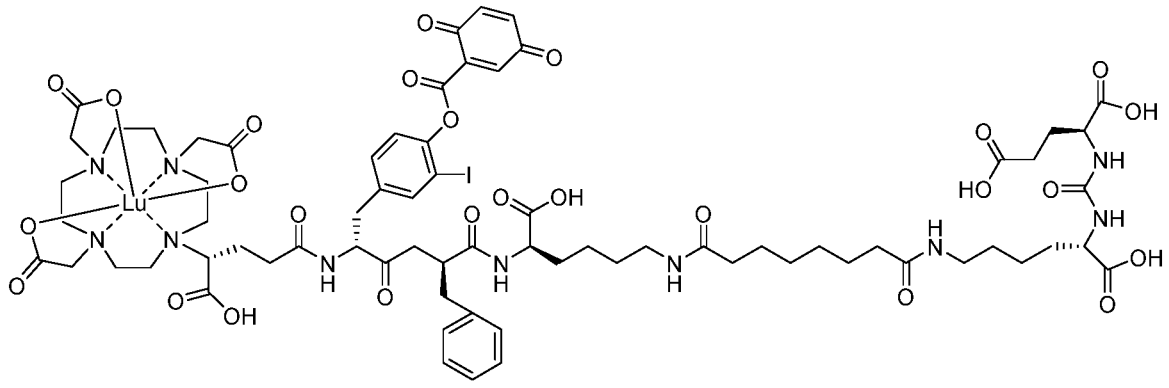


Scheme 1

That benzoquinone then may covalently couple with EuK-Sub-kf-iodo-y-DOTAGA during the incorporation reaction, for example to produce Adduct Compound Structures A1 and/or A2 (mass 1803 g/mol) as gentisate adduct impurities.



Adduct Compound Structure A1



Adduct Compound Structure A2

In a further aspect, suitably a composition (sometimes referred herein as the Formulation Composition and distinct from the Reaction Composition) is added following or upon termination of heating of the lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA particularly where a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA has been formed.

In particular, we have found enhanced stability and shelf-life of the formed ^{177}Lu-PSMA I&T can be achieved by treatment of the incorporation reaction composition with one or more gentisate compounds following or upon termination of the reaction heating step.

Thus, methods are providing for preparing ^{177}Lu-PSMA I&T, comprising a) admixing 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA; b) heating the admixed 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA, wherein a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is formed; and c) adding one or more ascorbate compounds while or after the heating is reduced or terminated. In certain aspects, both 1) one or more gentisate compounds and 2) one or more ascorbate compounds are added while or after the heating is reduced or terminated.

In a particular preferred embodiment, a gentisate compound is added to the formed complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA promptly after the termination of the heating step, for example within 0.25, 0.5, 1 or 2 minutes of initiation of termination (complete removal of heating source, or the occurrence of an at least 20°C

temperature drop) of the lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA incorporation reaction.

In yet a further preferred embodiment, both 1) a gentisate compound and 2) an ascorbate compound are added to the formed complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA promptly after the termination of the heating step, for example within 0.25, 0.5, 1 or 2 minutes of initiation of termination (complete removal of heating source, or the occurrence of an at least 20°C temperature drop) of the lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA incorporation reaction.

In an additional embodiment, preferably an ascorbate compound is added to the formed complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA promptly after the termination of the heating step, for example within 0.25, 0.5, 1 or 2 minutes of initiation of termination (complete removal of heating source, or the occurrence of an at least 20°C temperature drop) of the lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA incorporation reaction.

Such a post-heating Formulation Composition may be an aqueous composition comprising one or more gentisate compounds and/or one or more ascorbate compounds.

In certain aspects, following the lutetium-177 incorporation reaction, the produced ^{177}Lu-PSMA I&T may be first treated with one or more ascorbate compounds in the absence of a gentisate compound and subsequent to such ascorbate compound treatment the ^{177}Lu-PSMA I&T may be treated (e.g. admixed) with one or more gentisate compounds. In other aspects, following the lutetium-177 incorporation reaction, the produced ^{177}Lu-PSMA I&T may be treated substantially simultaneously with one or more ascorbate compounds and one or more gentisate compounds. For instance, an aqueous formulation comprising both ascorbic acid or salt thereof or other ascorbate compound and gentisic acid or salt thereof or other gentisate compound may be added to the formed complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA promptly after the termination of the heating step.

The aqueous admixture of the ^{177}Lu-PSMA I&T and one or more gentisate compounds and optionally one or more ascorbate compounds can be stored until administration to a patient.

As discussed, it has been found that such post-incorporation reaction use of one or more ascorbate compounds can provide enhanced stability and shelf life of the ^{177}Lu-PSMA I&T. See, for instance, Examples 1 and 2 which follow.

It has been further found that such post-incorporation reaction use of one or more ascorbate compounds in combination with one or more gentisate compounds can provide enhanced stability and shelf life of the ^{177}Lu-PSMA I&T. See, for instance, Examples 1 and which follow.

As referred to herein, an ascorbate compound or composition suitably may include for example ascorbic acid and/or an ascorbate salt such as sodium L-ascorbate, among others.

A gentisate compound or composition as referred to herein includes for example gentisic acid (2,5-dihydroxybenzoic acid). The term gentisate compound or composition also includes salts and esters of gentisic acid. A variety of gentisic acid salts may be suitably utilized as disclosed herein including for instance alkali metal, alkaline earth metal, and ammonium salts. Sodium and potassium salts may be preferred in some aspects. Ester compounds also may be utilized in certain aspects including for instance compounds esterified at one or both of the gentisic acid hydroxyl groups, such as compounds that have the 2-hydroxyl and/or 5-hydroxyl moieties functionalized with a methyl ester, ethyl ester or other C_{1-6}alkyl esters. In at least certain aspects, preferred gentisate compounds or compositions include gentisic acid or a gentisic acid salt.

In another aspect, methods are provided for preparing ^{177}Lu-PSMA I&T that include admixing lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA; and heating the lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA admixture for less than 30 minutes, including 25 or 20 minutes or less. The lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA admixture suitably can be heated for even shorter periods such as up to or less than 18

minutes, or up to or less than 16, 15, 14, 13, 12, 11,10, 9 or 8 minutes. In general heating for between 5 and 12 minutes can be suitable, at temperatures that include up to or less than 99 °C, 98°C, 97°C, 96°C, 95°C, 94°C, 93°C, 92°C, 91°C or 90°C. A reaction temperature of up to 40°C, 45°C, 50°C, 55°C, 60°C, 65°C, 70°C, 75°C, 80°C, 85°C, 90°C or 95°C may be suitable in certain aspects. Suitably, the lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA are heated as an aqueous mixture.

It has been found that such relatively mild reaction temperatures can provide high levels (e.g., at least 98, 99, 99.5 or 99.8 mole percent) incorporation of lutetium-177 and the precursor compound EuK-Sub-kf-iodo-y-DOTAGA (structures 1A and/or 1B above) together with a reduced impurity profile. As noted, ^{177}Lu-PSMA I&T (structures 2A and/or 2B above) is now provided for the first time at the high purities as disclosed herein, including with the absence of prior impurities.

In preferred aspects, the incorporation of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA includes at least one of the following 1), 2, 3) or 4) and preferably at least 1) and 2), more preferably at least 1), 2) and 3) and still more preferably each of the following 1), 2), 3) and 4):

1) inclusion of one or more ascorbate compound in the lutetium-177 incorporation reaction mixture. Optionally one or more gentisate compounds also may be present in the lutetium-177 incorporation reaction mixture, but such inclusion of gentisate compound is less preferred as discussed. Thus, particularly preferred is inclusion of one or more ascorbate compound in the lutetium-177 incorporation reaction mixture and without the inclusion of a gentisate compound;

2) a short heat treatment such up to or less than 30, 25, 20, 15, 12, 10 or 8 minutes as described above;

3) heating temperatures of the incorporation reaction mixture such as up to or less than 40°C, 45°C, 50°C, 55°C, 60°C, 65°C, 70°C, 75°C, 80°C, 85°C, 90°C or 95°C; and

4) a post-heating treatment (addition) with one or more gentisate compounds and/or one or more ascorbate compounds and preferably one or more gentisate compounds.

Such treatments 1), 2), 3) and/or 4) can provide highly pure ^{177}Lu-PSMA I&T (structures

2A and/or 2B above) with notable absence of one or more prior impurities together with high levels of lutetium-177 incorporation. See, for instance, the results set forth in Example 1 which follows.

In a further aspect, pharmaceutical compositions are provided. Preferred pharmaceutical compositions including aqueous formulations that comprise a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA (particularly ^{177}Lu-PSMA I&T having an optical excess of structure 2A) in the high purities as disclosed herein.

Preferred pharmaceutical compositions also may be aqueous compositions that include 1) a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA (particularly ^{177}Lu-PSMA I&T having an optical excess of structure 2A) and 2) one or more ascorbate compounds. In one aspect, such pharmaceutical compositions may not contain any other stabilizer compounds. In other aspects, such pharmaceutical compositions may contain one or more stabilizer compounds in addition to one or more ascorbate compounds.

Preferred pharmaceutical compositions also include aqueous compositions that include 1) a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA (particularly ^{177}Lu-PSMA I&T having an optical excess of structure 2A) and 2) i) one or more ascorbate compounds and ii) one or more gentisate compounds.

The one or more ascorbate compounds may be suitably present in a pharmaceutical composition in varying amounts, such as 5 or 10 mg/mL to 120 mg/mL; or 30 mg/mL to 100 mg/mL; or 40 mg/mL to 80 or 90 mg/mL. In a particular preferred aspect, the one or more ascorbate compounds such as an ascorbate salt may be present in an amount of 55 mg/mL to 75 mg/mL.

As discussed, the one or more ascorbate compounds may be incorporated both as a component of the lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA incorporation reaction as well as once the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA has been formed.

In such multiple additions to provide a desired amount of ascorbate compound(s) in a final ^{177}Lu-PSMA I&T pharmaceutical composition, a Reaction Composition may contain one or more ascorbate compounds such as ascorbic acid and/or an ascorbate salt in an amount of 5 or 10 mg/mL to 120 mg/mL; or 5 or 10 mg/mL to 100 or 110 mg/mL; or 5 or 10 mg/mL to 80 or 90 mg/mL, in a particular preferred aspect, the one or more ascorbate compounds such as ascorbic acid and/or an ascorbate salt may be present in an amount of 55 mg/mL to 75 mg/mL.

Additionally, one or more ascorbate compounds such as ascorbic acid and/or an ascorbate salt may be added to a formed complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA to provide a pharmaceutical formulation containing that formed complex wherein a total amount of ascorbate compound(s) is for example 5 or 10 mg/mL to 100 mg/mL in the formulation; or 5 or 10 mg/mL to 60 or 80 mg/mL in the formulation; or 5 or 10 mg/mL to 40 or 50 mg/mL in the formulation. In a particular preferred aspect, the one or more ascorbate compounds such as ascorbic acid and/or an ascorbate salt may be present in an amount of 55 mg/mL to 75 mg/mL in such formulation containing that formed complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA. In a further preferred aspect, the one or more ascorbate compounds such as ascorbic acid and/or an ascorbate salt may be present in lower amounts of amount of 10 mg/mL or 15mg/mL to 20 mg/mL, 25 mg/mL, 30 mg/mL, 40 mg/mL, 45 mg/mL, 50 mg/mL, or 55 mg/mL, in such formulation containing that formed complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA. In certain preferred aspect, the one or more ascorbate compounds such as ascorbic acid and/or an ascorbate salt may be present in amounts up to 10 mg/mL, 15 mg/mL, 20 mg/mL, 25 mg/mL, 30 mg/mL, 35 mg/mL, 40 mg/mL, 45 mg/mL, 50 mg/mL, 55 mg/mL, 60 mg/mL, 65 mg/mL, 70 mg/mL, 75 mg/mL, 80 mg/mL, 85 mg/mL, 90 mg/mL, 95 mg/mL or 100 mg/mL or more in such formulation containing that formed complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA.

In a pharmaceutical composition that contains a gentisate compound, one or more gentisate compounds suitably may be present such as gentisic acid or a gentisate salt in an amount of for example 5 or 10 mg/mL to 100 mg/mL; or 5 or 10 mg/mL to 60 or 80

mg/mL; or 5 or 10 mg/mL to 40 or 50 mg/mL. In a particular preferred aspect, the one or more gentisate compounds such as a gentisate salt may be present in an amount of 16 mg/mL to 36 mg/mL. As discussed, such amounts of one or more gentisate compounds may be preferably added to a formed complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA while or after heating, in the heating step of the incorporation reaction, is reduced or terminated. As also discussed, the one or more gentisate compounds may be preferably added to a formed complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA in combination with an ascorbate compound that is either already present with the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA , and/or a combination of a gentisate compound and an ascorbate compound are added in combination to a formed complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA. In certain preferred aspect, the one or more gentisate compounds such as gentisic acid may be present in amounts up to 1 mg/mL, 2 mg/mL, 3 mg/mL, 4 mg/mL, 5 mg/mL, 6 mg/mL, 7 mg/mL, 8 mg/mL, 9 mg/mL, 10 mg/mL, 15 mg/mL, 20 mg/mL, 25 mg/mL, 30 mg/mL, 35 mg/mL, 40 mg/mL, 45 mg/mL, 50 mg/mL, 55 mg/mL, 60 mg/mL, 65 mg/mL, 70 mg/mL, 75 mg/mL, 80 mg/mL, 85 mg/mL, 90 mg/mL, 95 mg/mL or 100 mg/mL or more, in such formulation containing that formed complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA.

In the present pharmaceutical compositions, a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA (including, a compound of structure 2A above) also may be present in varying concentrations, such as to provide a volumetric radioactivity of at least 100 MBq/mL, preferably of at least 250, 300, 400, 500, 600, 700, 800, 900, 1000, 1200, 1400, 1600, 1800 or 2000 MBq/mL for 0.5, 1, 2, 3, 4 or 5 days following preparation of the pharmaceutical composition.

In certain aspects, a pharmaceutical composition does not contain a gentisate compound. In certain aspects, a pharmaceutical composition does not contain any other stabilizer agent other than one or more ascorbate compounds. Preferably, the radiochemical purity of a pharmaceutical composition is at least 95%, 96%, 97%, 98% or 99% for 3, 4 or 5 days or more at a temperature of 30°C or less following preparation of the composition. Even more preferably, the radiochemical purity of a pharmaceutical

composition is at least 96%, 97% or 98% for 3, 4 or 5 days or more at a temperature of 30°C or less following preparation of the composition.

In a further aspect, a compound comprising a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is provided, i.e. ^{177}Lu-PSMA I&T including ^{177}Lu-PSMA I&T having an optical excess of structure 2A above, wherein the complex is:

1) free of unchelated lutetium-177 in an amount of not more than 2, 1.5, 1.0 or 0.5 weight % based on total weight of the ^{177}Lu-PSMA I&T, such as may be determined by radiometric detection (including HPLC radiometric detection); and/or

2) free of radiochemical impurities in an amount of not more than 5, 4, 3.5, 3, 2.5, 2, 1.5, 1.0 or 0.5 weight % based on total weight of the ^{177}Lu-PSMA I&T, such as may be determined by radiometric detection (including HPLC radiometric detection); and/or

3) free of chemical impurities in an amount of not more than 5, 4, 3, 2, 1 or 0.5 weight %, all weight % based on total weight of the ^{177}Lu-PSMA I&T, such as may be determined by HPLC/UV analysis, and where the ^{177}Lu-PSMA I&T is maintained at 30°C or less and such purity levels are exhibited for 3, 4 or 5 days or more following preparation of the ^{177}Lu-PSMA I&T.

In a yet further aspect, a compound comprising a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is provided, i.e. ^{177}Lu-PSMA I&T including ^{177}Lu-PSMA I&T having an optical excess of structure 2A above, wherein the complex is:

1) free of unchelated lutetium-177 in an amount of not more than 2, 1.5, 1.0 or 0.5 weight % based on total weight of the ^{177}Lu-PSMA I&T, such as may be determined by radiometric detection (including HPLC radiometric detection); and/or

2) free of radiochemical impurities in an amount of not more than 5, 4, 3.5, 3, 2.5, 2, 1.5, 1.0 or 0.5 weight % based on total weight of the ^{177}Lu-PSMA I&T, such as may be determined by radiometric detection (including HPLC radiometric detection); and/or

3) free of chemical impurities including a gentisate adduct impurity in an amount of not more than 5, 4, 3, 2, 1 or 0.5 weight %, all weight % based on total weight of the ^{177}Lu-PSMA I&T, such as may be determined by HPLC/UV analysis, and where the ^{177}Lu-

PSMA I&T is maintained at 30°C or less and such purity levels are exhibited for 3, 4 or 5 days or more following preparation of the ^{177}Lu-PSMA I&T.

Suitably, the compound may be present in an aqueous formulation. As understood, a radiochemical impurity will contain lutetium-177 or a degradation species thereof, while a chemical impurity may or may not contain lutetium-177 or a degradation species thereof. Amounts of radiochemical and chemical impurities as referred to herein can be assessed by chromatography including HPLC.

In a still further aspects, ^{177}Lu-PSMA I&T (including structures 2A and/or 2B above) is provided as obtainable by or obtained from a process disclosed herein, including a process for the incorporation lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA comprising at least one of the following 1), 2) or 3) and preferably at least 1) and 2) and more preferably each of the following 1), 2) and 3):

1) inclusion of one or more ascorbate compound in the lutetium-177 incorporation reaction mixture. Optionally one or more gentisate compounds also may be present in the lutetium-177 incorporation reaction mixture, but such inclusion of gentisate compound is less preferred as discussed. Thus, particularly preferred is inclusion of one or more ascorbate compound in the lutetium-177 incorporation reaction mixture and without the inclusion of a gentisate compound;

2) a short heat treatment such up to or less than 30, 20, 15, 12, 10 or 8 minutes as described above; and

3) a post-heating treatment (addition) with one or more gentisate compounds and/or one or more ascorbate compounds and preferably one or more gentisate compounds.

Methods of treatment are also provided including to treat a subject that is suffering from a cell proliferative disease or disorder, particularly a cancer by administering to the subject an effective amount of ^{177}Lu-PSMA I&T. In particular aspects, ^{177}Lu-PSMA I&T having an optical excess of structure 2A is administered.

In particular, the present ^{177}Lu-PSMA I&T and compositions, including ^{177}Lu-PSMA I&T having an optical excess of structure 2A above, may be used to treat a subject

suffering from prostate cancer, including metastatic castration-resistant prostate cancer (such as may be manifested by progression of the disease despite prior surgical or chemical castration) including those subjects that have progressed following treatment with androgen receptor-axis-targeted (ARAT) therapies.

In one aspect, methods for treating a patient such as a human suffering from cancer, comprising: a) admixing 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA in the substantial or complete absence of a gentisate compound; b) heating the admixed 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA in the substantial or complete absence of a gentisate compound, wherein a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is formed; and c) administering the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA to patient. Suitably, 1) lutetium-177, 2) EuK-Sub-kf-iodo-y-DOTAGA and 3) one or more stabilizer compounds are admixed in the absence of a gentisate compound. Suitably, 1) lutetium-177, 2) EuK-Sub-kf-iodo-y-DOTAGA and 3) one or more stabilizer compounds are heated in the absence of a gentisate compound.

Uses of the present complexes of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA to treat a patient (such as human) suffering from cancer are also provided, wherein the complex is obtained or obtainable from a) admixing 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA in the substantial or complete absence of a gentisate compound; and b) heating the admixed 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA in the substantial or complete absence of a gentisate compound, wherein a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is formed. Suitably, 1) lutetium-177, 2) EuK-Sub-kf-iodo-y-DOTAGA and 3) one or more stabilizer compounds are admixed in the absence of a gentisate compound. Suitably, 1) lutetium-177, 2) EuK-Sub-kf-iodo-y-DOTAGA and 3) one or more stabilizer compounds are heated in the absence of a gentisate compound.

In a further aspect, kits are provided for ^{177}Lu-PSMA I&T, including cold kits where the ^{177}Lu-PSMA I&T can be prepared shortly before administration such as in a medical facility, for example a hospital laboratory or nuclear pharmacy. In such a kit, EuK-Sub-kf-iodo-y-DOTAGA (structures 1A and/or 1B) may be provided in a vial or other container in lyophilized or other form separate from lutetium-177. The EuK-Sub-

kf-iodo-y-DOTAGA and lutetium-177 are reacted as disclosed herein at the medical facility to provide ^{177}Lu-PSMA I&T (including ^{177}Lu-PSMA I&T having an optical excess of structure 2A) which then can be promptly administered to a patient. Such kits including cold kits may comprise components such as, for example, one or more buffering agents such as an acetate compound and/or one or more radioprotectants or stabilizer agents such as ascorbate compound and a gentisate compound.

In a yet further aspect, packaged preparations or products of ^{177}Lu-PSMA I&T (including ^{177}Lu-PSMA I&T having an optical excess of structure 2A above)) are provided. A packaged preparation may comprise 1) ^{177}Lu-PSMA I&T (including ^{177}Lu-PSMA I&T having an optical excess of structure 2A) and optionally 2) instructions for using ^{177}Lu-PSMA I&T (including ^{177}Lu-PSMA I&T having an optical excess of structure 2A) for treating a cancer such as prostate cancer. Preferably, the packaged preparation will comprise a therapeutically effective amount of ^{177}Lu-PSMA I&T (including ^{177}Lu-PSMA I&T having an optical excess of structure 2A). The instructions suitably may be in written form, including as a packaging label. The ^{177}Lu-PSMA I&T (including ^{177}Lu-PSMA I&T having an optical excess of structure 2A) suitably may be contained within a lead vessel or other container that is within further packaging that may include product identification, instructions for use or other information.

Other aspects of the invention are disclosed *infra*.

BRIEF DESCRIPTION OF FIGURES

FIG. 1A shows an exemplary reaction with acetate and gentisate (peak at 10.2 min consistent with the gentisate adduct impurity always appears) – 20 min reactions at 90°C min as detailed in Example 1 which follows.

FIGS. 1A-1C show exemplary reactions with ascorbate and gentisate (peak at 10.2 min consistent with the gentisate adduct impurity appears) – 20 min reactions at 90°C as detailed in Example 1 which follows.

FIG. 1D shows an exemplary reaction with just ascorbate (peak at ~10.2 min consistent with the gentisate adduct impurity never appears) – 20 min reactions at 90°C as detailed in Example 1 which follows.

FIGS. 1E and 1F show HPLC chromatograms of Example 2 which follows.

FIG. 2 shows schematically the general synthesis and formulation of ^{177}Lu-PSMA I&T in Example 2 which follows.

DETAILED DESCRIPTION

In one aspect, new pharmaceutical compositions are provided that comprise: (a) a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA; and (b) one or more ascorbate compounds.

Preferably, the pharmaceutical composition is free of a gentisate adduct impurity.

Suitably, the pharmaceutical composition is an aqueous formulation.

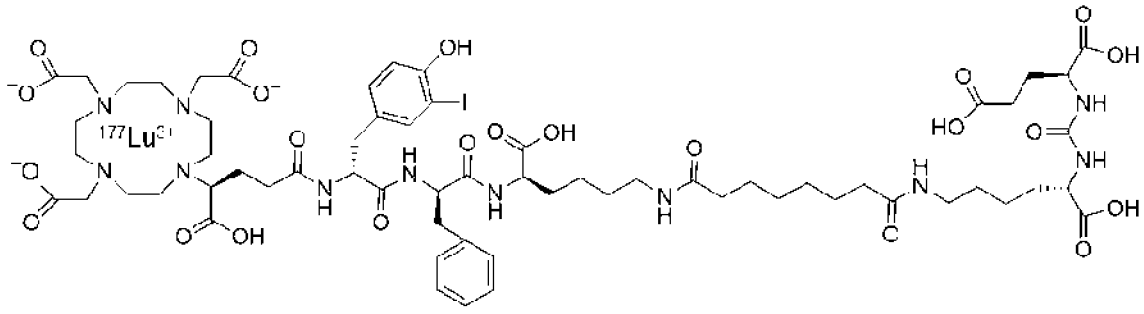
In one embodiment, the pharmaceutical composition at least substantially free of a gentisate compound. In another embodiment, the pharmaceutical composition comprises one or more gentisate compounds. In a further embodiment, the pharmaceutical composition comprises one or more stabilizers in addition to one or more ascorbate compounds.

In a further aspect, new pharmaceutical compositions are provided that comprise (a) a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA; and (b) one or more stabilizer compounds, wherein the composition at least substantially free of a gentisate compound. Preferably, the pharmaceutical composition is an aqueous formulation. Suitably, the one or more stabilizers comprise one or more ascorbate compounds. In one embodiment, the pharmaceutical composition at least substantially free of a gentisate compound. In a further embodiment, the pharmaceutical composition comprises one or more stabilizers in addition to one or more ascorbate compounds.

In a further aspect, new pharmaceutical compositions are provided that comprise (a) a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA; (b) one or more stabilizer compounds, wherein the composition is at least substantially free of a gentisate adduct impurity. As referred to herein, a pharmaceutical composition or complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is at least substantially free of a gentisate adduct impurity if an HPLC does not show the presence of a peak (e.g. by visible review of spectra) being present in the 9 to 12 minute region of an HPLC chromatogram corresponding, in particular aspects the 9 or 9.5 to 10.5 or 11 minute region or the about 10.2 minute region as exemplified by the radio chromatograms of FIGS. 1C and 1D, as discussed above.

Preferably, the pharmaceutical composition is an aqueous formulation. Suitably, the one or more stabilizers comprise one or more ascorbate compounds. In one embodiment, the pharmaceutical composition at least substantially free of a gentisate compound. In another embodiment, the pharmaceutical composition comprises one or more gentisate compounds. In a further embodiment, the pharmaceutical composition comprises one or more stabilizers in addition to one or more ascorbate compounds.

In a preferred embodiment, in the above pharmaceutical compositions, the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA comprises the following structure:



Preferably, in the above pharmaceutical compositions, the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is:

1) free of unchelated lutetium-177 in an amount of 1 weight % or less; and/or

2) free of radiochemical impurities in an amount of 3 weight % or less; and/or

3) free of chemical impurities in an amount of 5 weight % or less,

all weight % based on total weight of the ^{177}Lu-PSMA I&T, and

where complex is maintained at 30°C or less and such purity levels are exhibited for 3, 4 or 5 days or more following preparation of the complex.

Preferably, in the above pharmaceutical compositions, a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is present in a therapeutically effective amount, e.g., in a unit dosage or multiple dosages as disclose herein.

Preferably, in the above pharmaceutical compositions, one or more stabilizer compounds such as one or more ascorbate compounds are present in an effective amount in the pharmaceutical composition, for example to provide stability and purity levels as disclosed herein, such as a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is present in a therapeutically effective amount, e.g., in a unit dosage or multiple dosages as disclose herein, such as where a composition maintained at 30°C or less desired purity levels are exhibited for 3, 4 or 5 days or more following preparation of the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA. The exemplary stabilizer compound amounts disclosed herein are preferred in certain aspects.

In certain aspects, in the above pharmaceutical compositions, and methods disclosed herein, an optical excess of a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is present or utilized such as an optical excess of a compound of structure 2A above or an optical excess of a compound of structure 2B above. In additional certain aspects, the above pharmaceutical compositions, and methods disclosed herein, a substantial optical excess of a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is present or utilized such as a substantial optical excess of a compound of structure 2A above or a substantial optical excess of a compound of structure 2B above.

In further aspects, methods for preparing ^{177}Lu-PSMA I&T are provided that comprise: a) admixing 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA; and b) heating the admixed 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA for 15 minutes or less; wherein a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is formed.

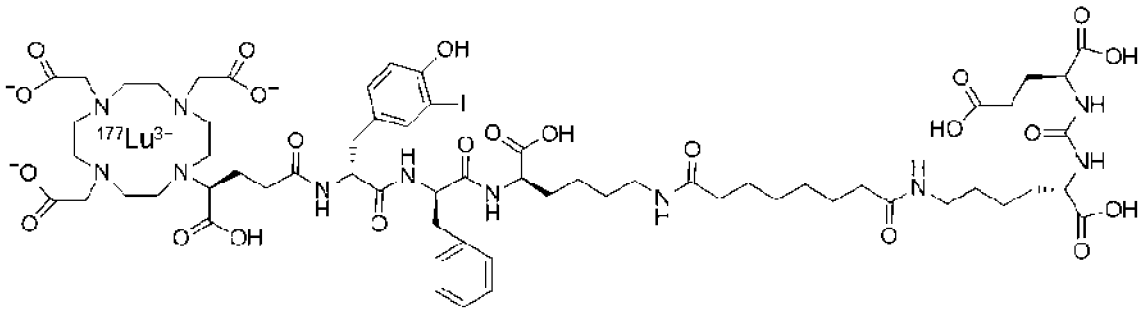
Preferably the admixed 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA are at least substantially free of a gentisate compound during the b) heating. Preferably, one or more ascorbate compounds are admixed with the 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA.

In further preferred aspects, the methods may further comprise adding one or more gentisate compounds to the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA, for example where such one more ascorbate compounds are added upon reduction or termination of heat.

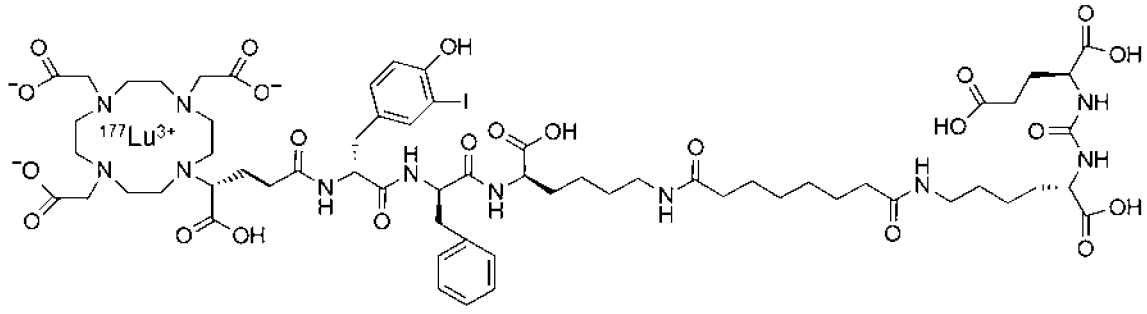
In still further preferred aspects, the methods may further comprise adding one or more gentisate compounds and/or one or more ascorbate compounds to the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA, for example where such one or more gentisate compounds and/or one or more ascorbate compounds are added upon reduction or termination of heat.

Methods are also provided for preparing ^{177}Lu-PSMA I&T, comprising a) admixing 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA; b) heating the admixed 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA, wherein a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is formed; and c) adding one or more ascorbate compounds while or after the heating is reduced or terminated. In certain aspects, both 1) a gentisate compound and 2) an ascorbate compound are added while or after the heating is reduced or terminated. Suitably, an admixture of 1) lutetium-177, 2) EuK-Sub-kf-iodo-y-DOTAGA, and 3) one or more stabilizers are heated, wherein a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is formed.

^{177}Lu-PSMA I&T is a lutetium-177 complex of the above structures 1A and/or 1B and may be represented by the following structures 2A and/or 2B:



2A



2B

^{177}Lu-PSMA I&T also has a chemical name of suber-1-oyl-Ɛ-(DOTA-GA-3-iodo-D-Tyr-D-Phe-D-Lys-OH)-8-oyl- Ɛ-(HO-Glu-ureido-Lys-OH); lutetium-177(3^{+}). ^{177}Lu-PSMA I&T has a molecular formula of $C_{63}H_{89}{}^{177}LuIN_{11}O_2$ and molecular mass of 1672.29 g/mol.

The present invention, including compounds, methods, and pharmaceutical compositions/formulations will be described with reference to the following definitions which, for convenience, are set forth below. Unless otherwise specified, the below terms used herein are defined as follows:

I. Definitions

As used herein, the term "a," "an," "the" and similar terms used in the context of the present invention (especially in the context of the claims) are to be construed to cover

both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

The language “and/or” is used herein as a shorthand notation to represent the expression “and,” describing the combination of items, as well as “or,” describing the items in the alternative form.

Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

The term "about", as used herein, means an acceptable margin of error for a particular value, which depends in part on how the value is measured or determined. In certain embodiments, “about” as used herein will be understood by persons of ordinary skill in the art to mean up to plus or minus 20% of the particular term. In further embodiments, “about” as used herein will be understood by persons of ordinary skill in the art to mean up to plus or minus 10% of the particular term.

As used herein, the term “optically enriched” or “optical excess” denotes the presence of one or more non-racemic stereoisomeric centers in a molecule, wherein the configuration of at least one stereoisomeric center has a predominance of one stereoisomeric configuration (R or S). For example, one stereoisomeric center in a molecule, typically a carbon atom, may have greater than 50 or 55 weight % (based on total weight of the compound) of its attached atoms spatially arranged in the (R) configuration. Alternatively, more than 50 weight % (based on total weight of the compound) may be spatially arranged in the (S) configuration. More preferably the molecule, or its stereoisomeric center, is substantially optically enriched, and even more preferably is substantially enantiomerically pure.

As used herein, the term “substantially optically enriched” or “substantial optical excess”, when referring to a stereoisomer or stereoisomeric center, denotes that at least about 60 weight % (based on total weight of the compound), preferably about 70 weight

% (based on total weight of the compound), more preferably about 80 weight % (based on total weight of the compound), still more preferably about 90 weight % (based on total weight of the compound) of one stereoisomer or one stereoisomeric center configuration predominates in the mixture, with at least about 95 weight % (based on total weight of the compound) of one stereoisomer or one stereoisomeric center configuration being even more preferred. In some preferred embodiments, the compound is “substantially enantiomerically pure”, that is, at least about 97.5 weight % (based on total weight of the compound), more preferably about 99 weight % (based on total weight of the compound), even more preferably about 99.5 weight % (based on total weight of the compound) of one stereoisomeric configuration predominates.

As used herein, the term "substantially pure" means sufficiently homogeneous to appear free of readily detectable impurities as determined by standard analytical methods, such as thin layer chromatography (TLC), gel electrophoresis, high performance liquid chromatography (HPLC), nuclear magnetic resonance (NMR), and mass spectrometry (MS); or sufficiently pure such that further purification would not detectably alter the physical and chemical properties, or biological and pharmacological properties, such as enzymatic and biological activities, of the substance. In certain embodiments, "substantially pure" refers to a collection of molecules, wherein at least about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 97%, about 98%, about 98.5%, about 99%, about 99.5% or about 99.9% or greater of the molecules are a single compound, including a racemic mixture or a single stereoisomer thereof, as determined by standard analytical methods.

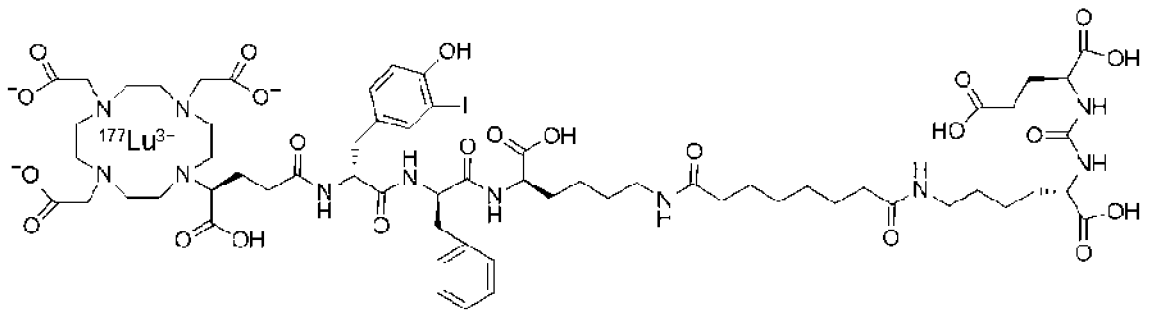
As used herein, and unless otherwise specified, the terms "treat," "treating" and "treatment" refer to the eradication or amelioration of a disease, disorder, or condition, or of one or more symptoms associated with the disease, disorder or condition. In certain embodiments, the terms refer to minimizing the advancement or worsening of the disease, disorder, or condition resulting from the administration of a formulation of the invention to a patient with such a disease, disorder, or condition. In some embodiments, the terms refer to the administration of a formulation provided herein, after the onset of symptoms

of the particular disease, disorder, or condition. The terms "treat," "treating", "treatment", or the like, as used herein covers the treatment of a disease, disorder, or condition in a subject, *e.g.*, a mammal, and includes at least one of: (i) inhibiting the disease, disorder, or condition, *i.e.*, partially or completely halting its progression; (ii) relieving the disease, disorder, or condition, *i.e.* causing regression of symptoms of the disease, disorder, or condition, or ameliorating a symptom of the disease, disorder, or condition; and (iii) reversal or regression of the disease, disorder, or condition, preferably eliminating or curing of the disease, disorder, or condition. In a particular embodiment the terms "treat," "treating", "treatment", or the like, covers the treatment of a disease, disorder, or condition in a mammal, *e.g.*, a primate, *e.g.*, a human, and includes at least one of (i), (ii), and (iii) above. As is known in the art, adjustments for age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition may be necessary, and will be ascertainable with routine experimentation by one of ordinary skill in the art based on the invention described herein.

As used herein, the terms "subject", and "patient" are used interchangeably. The terms "subject" and "patient" refer to an animal such as a mammal including non-primates (*e.g.*, a cow, pig, horse, sheep, rabbit, guinea pig, rat, cat, dog, and mouse) and primates (*e.g.*, a monkey, chimpanzee and a human). In a particular embodiment, the subject is a human.

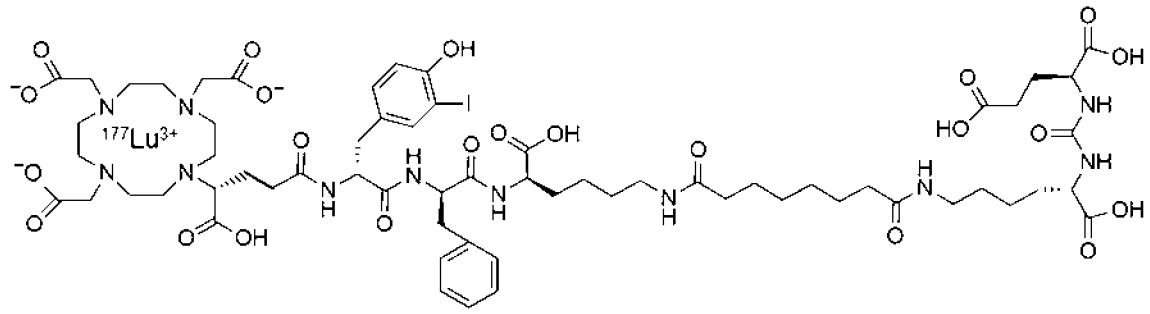
Syntheses

^{177}Lu-PSMA I&T (including structures 2A and/or 2B below) can be prepared by complexing or incorporating ^{177}Lu (lutetium-177) or halide thereof such as $^{177}LuCl_3$ with EuK-Sub-kf-iodo-y-DOTAGA (structures 1A and/or 1B below).



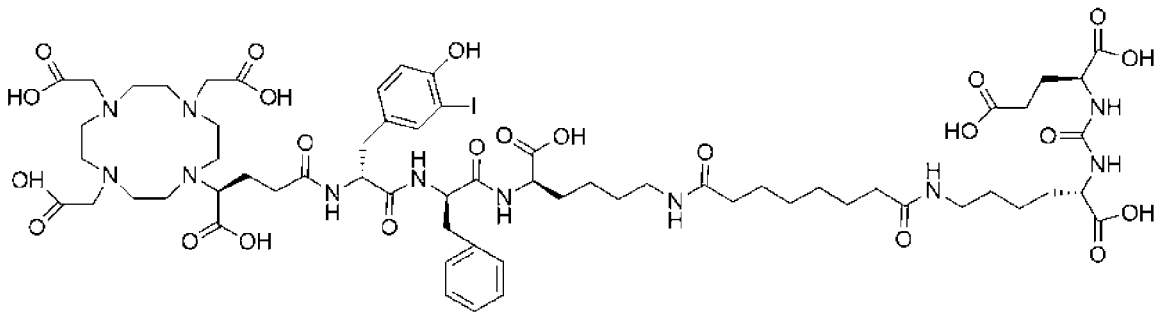
2A

An IUPAC designation of structure 2A is lutetate(5-)-177Lu, [N-[(4*S*)-4-(carboxy-KO)-4-[4,7,10- tris[(carboxy-KO)methyl]-1,4,7,10-tetraazacyclododec-1-yl-KN1,KN4,KN7,KN10]-1-oxobutyl]-3-iodo-D-tyrosyl-D-phenylalanyl-N6-[8- [[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-1,8-dioxooctyl]-D- lysinato(8-)]-, hydrogen (1:5).



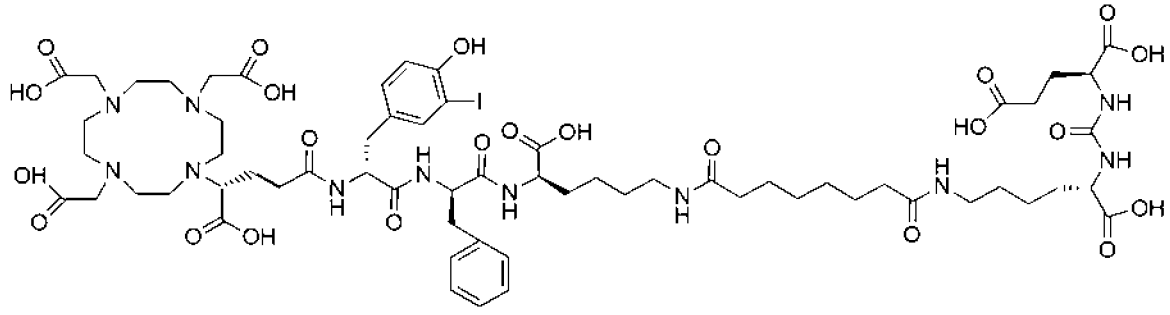
2B

An IUPAC designation of compound 2B is lutetate(5-)-177Lu,N-[(4*R*)-4-(carboxy-KO)-4-[4,7,10- tris[(carboxy-KO)methyl]-1,4,7,10-tetraazacyclododec-1-yl-KN1,KN4,KN7,KN10]-1-oxobutyl]-3-iodo-D-tyrosyl-D-phenylalanyl-N6-[8- [[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-1,8-dioxooctyl]-D- lysinato(8-)]-, hydrogen (1:5).



1A

The *S* isomer compound of structure 1A has an IUPAC name of N-[(4*S*)-4-(carboxy-KO)-4-[4,7,10- tris[(carboxy-KO)methyl]-1,4,7,10-tetraazacyclododec-1-yl-KN1,KN4,KN7,KN10]-1-oxobutyl]-3-iodo-D-tyrosyl-D-phenylalanyl-N6-[8- [[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-1,8-dioxooctyl]-D-lysinato(8-)]-, hydrogen (1:5)).



1B

The *R* isomer compound of structure 1B has an IUPAC name of: [N-[(4*R*)-4-(carboxy-KO)-4-[4,7,10- tris[(carboxy-KO)methyl]-1,4,7,10-tetraazacyclododec-1-yl-KN1,KN4,KN7,KN10]-1-oxobutyl]-3-iodo-D-tyrosyl-D-phenylalanyl-N6-[8- [[(5S)-5-carboxy-5-[[[[(1S)-1,3-dicarboxypropyl]amino]carbonyl]amino]pentyl]amino]-1,8-dioxooctyl]-D- lysinato(8-)]-, hydrogen (1:5)).

The structures 1A and/or 1B may be suitably formed as described previously such as in Weineisen et al. *J Nucl Med* 2015; 56:1169–1176; and Chatalic, *Theranostics*, 6(6), 849-861 (2016). To provide an optically enriched or substantially optically enriched or

enantiomerically pure sample of ^{177}Lu-PSMA I&T the corresponding optical isomer of EuK-Sub-kf-iodo-y-DOTAGA may be used in the incorporation reaction. That is, the compound of structure 1A may be reacted with lutetium-177 to provide the *S* isomer complex of structure 2A, and the compound of structure 1B may be reacted with lutetium-177 to provide the *R* isomer complex of structure 2B. The structures 1A and/or 1B also are available from piCHEM (RaabaGrambach, Austria). Optically enriched mixtures of structures 1A and/or 1B suitably may be prepared with use of an optically enriched precursor (reagent) and/or separation of optical isomers with an appropriate optically active reagent such as an optically active salt.

It is understood that ^{177}Lu-PSMA I&T as referred to herein includes the above structures 2A and/or 2B as well as other complexes of lutetium (^{177}Lu) and EuK-Sub-kf-iodo-y-DOTAGA. For instance, references herein to ^{177}Lu-PSMA I&T include compounds that generally correspond to structure 2A and/or 2B but where the ^{177}Lu substantially complexes to other portions or moieties (such as one or more other nitrogens) of the EuK-Sub-kf-iodo-y-DOTAGA molecule than as depicted in structures 2A and 2B above. References to ^{177}Lu-PSMA I&T also may include other stereoisomers than those shown in structures 1A, 1B, 2A, and 2B above, although the stereoisomers depicted in structures 1A, 1B, 2A, and 2B are preferred, particularly structures 1A and 2A.

To synthesize ^{177}Lu-PSMA I&T, lutetium-177 (^{177}Lu) can be admixed with EuK-Sub-kf-iodo-y-DOTAGA. The ^{177}Lu suitably may be carrier added or more preferably no-carrier-added (n.c.a.) lutetium-177. To facilitate incorporation (e.g. complexing including chelating) of lutetium-177 with the EuK-Sub-kf-iodo-y-DOTAGA compound, preferably an admixture of the compounds is thermally treated.

As discussed, it has been found that substantially complete incorporation of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA can be accomplished under comparatively mild conditions including relatively short heating times such as up to or less than 30, 25, 20, 15, 12, 10, 9, 8, 7, 6 or 5 minutes and/or reduced temperatures such as up to or less than 99°C, 98°C, 97°C, 96°C, 95°C, 94°C, 93°C, 92°C, 91°C or 90°C, or even lower temperatures for the incorporation reaction such as up to or less than 95°C, 90°C,

85°C, 80°C, 75°C, 70°C, 65°C, 60°C, 55°C, 50°C, 45°C or 40°C including for relatively short heating times such as up to or less than 30, 25, 20, 15, 12, 10 or 8 minutes.

In some embodiments, an admixture of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is heated for 20 minutes of less. In certain preferred embodiments, the admixture is heated for 15 minutes of less. In certain preferred embodiments, the admixture is heated for 12 minutes of less. In certain preferred embodiments, the admixture is heated for between about 8 and 12 minutes. For example, the admixture is heated for up to or less than about 8 minutes, for up to or less than about 9 minutes, for up to or less than about 10 minutes, for up to or less than about 11 minutes, or for up to or less than about 12 minutes. In certain preferred embodiments, the admixture is heated for at least about 8, 9, 10, 11 or 12 minutes.

In some embodiments, an admixture of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is heated at about 98°C or less. In certain preferred embodiments, the admixture is heated at about 90°C $\pm$ 5°C. For example, the admixture is heated at about 85°C, at about 86°C, at about 87°C, at about 88°C, at about 89°C, at about 90°C, at about 91°C, at about 92°C, at about 93°C, at about 94°C, or at about 95°C. Lower temperatures for the lutetium-177 incorporation also may be employed such as up to or less than 95°C, 90°C, 85°C, 80°C, 75°C, 70°C, 65°C, 60°C, 55°C, 50°C, 45°C or 40°C including as discussed above for relatively short heating times such as up to or less than 30, 25, 20, 15, 12, 10 or 8 minutes.

In some embodiments, a formulation including EuK-Sub-kf-iodo-y-DOTAGA and one or more ascorbate compounds is admixed with lutetium-177. In certain preferred embodiments, an acidic aqueous formulation of lutetium-177 is admixed with EuK-Sub-kf-iodo-y-DOTAGA and one or more ascorbate compounds (a Reaction Composition comprising one or more ascorbate compounds).

As referred to herein, an ascorbate compound suitably may include for example ascorbic acid or an ascorbate salt such as sodium L-ascorbate, among others.

In certain preferred embodiments, a hydrogen halide or acid halide aqueous formulation of lutetium-177 is admixed with EuK-Sub-kf-iodo-y-DOTAGA, including together with one more ascorbate compounds. In certain preferred embodiments, a hydrochloride acid aqueous formulation of lutetium-177 is admixed with EuK-Sub-kf-iodo-y-DOTAGA, including with one or more ascorbate compounds.

It is generally preferred that admixture of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is agitated during heat treatment, for example the admixture is stirred or shaken during a portion or substantially all of the heat treatment.

In some embodiments, the produced complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA does not contain a gentisate adduct impurity that has a retention time of the 9 to 12 minute region, in particular aspects the 9 or 9.5 to 10.5 or 11 minute region or the about 10.2 minute region as shown in the spectra of FIGS. 1C and 1D and by HPLC analysis as defined herein, i.e. high-performance liquid chromatography with a Waters XBridge BEH Phenyl-Hexyl Column, 130Å, 3.5 μm, 4.6 mm X 150 mm using 0.1% trifluoracetic acid in water (Mobile Phase A) and 0.1% trifluoracetic acid in acetonitrile (Mobile Phase B), with a linear gradient from 85% Mobile Phase A to 55% Mobile Phase A being used over 12 minutes and the ratio was held for 15 minutes.

In some embodiments, the incorporation of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is greater than 98 mole percent. In certain preferred embodiments, the molar incorporation of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is greater than 99 mole percent, including 99.5, 99.6, 99.7, 99.8 and 99.9 mole percent.

In some embodiments, the radiochemical purity of the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA formulated as disclosed herein with one or more ascorbate compounds and optionally with one or more gentisate compounds is at least or up to 95%, 96%, 97% or 98% for 3, 4 or 5 days or more following the incorporation reaction and subsequent formulation with ascorbate compound(s) and optional gentisate compound(s) with storage of the ^{177}Lu-PSMA I&T at a temperature of 30°C or less.

Such levels of radiochemical purity and incorporation of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA can be provided by the reaction product of the syntheses disclosed herein and formulation of such reaction product with one or more ascorbate compounds and optionally one or more gentisate compounds without further treatment (particularly purification) step such as chromatography. Thus, significantly, the formulated lutetium-177 incorporation reaction admixture can be directly packaged (for example, stored in a sealed vial or IV bag) following formulation of the incorporation reaction product with such high purity ^{177}Lu-PSMA I&T without the need for a purification or other treatment step to remove impurities.

If desired however ^{177}Lu-PSMA I&T prepared as disclosed herein may be further treated following incorporation of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA, for example through HPLC or other chromatography or other purification treatment.

Preferred preparations of ^{177}Lu-PSMA I&T may include one or more and preferably each of the following steps 1-6:

1. Provide lutetium-177 such as in a vial that can serve as a reaction vessel. The lutetium-177 suitably may be present in an aqueous acidic formulation, such as an HCl formulation.

2. Admix EuK-Sub-kf-iodo-y-DOTAGA with an aqueous buffer composition (Reaction Composition) that contains one or more ascorbate compound such as one or more of sodium L-ascorbate and ascorbic acid.

3. Admix the EuK-Sub-kf-iodo-y-DOTAGA composition from step 2 with the lutetium-177 formulation of step 1. For example, the EuK-Sub-kf-iodo-y-DOTAGA composition can be added to a vial that contains the lutetium-177.

4. The admixture of step 3 containing EuK-Sub-kf-iodo-y-DOTAGA and lutetium-177 then can be heated preferably with agitation, for example shaking with heating at 40-99°C or 70-99°C, or 80-98°C for up to 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 minutes. Lower heating temperatures may be preferred, such as up to 40°C, 50°C, 60°C, 70°C, 80°C, 90°C or 95°C for up to 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 minutes.

5. At the end of the heating treatment of step 4, an aqueous composition (Formulation Composition) containing one or more ascorbate compounds and, in certain systems, one or more gentisate compounds, is added to the vial or other reaction vessel. For instance, within about 0.1, 0.25, 0.5, 1, 2, 3, 4 or 5 minutes after commencing reduction or termination of heating, an aqueous composition (Formulation Composition) containing one or more ascorbate compound is added to the vial or other reaction vessel. Reduction or termination of heating can include physical removal of the heating source from the reaction vessel, or termination of power to the heating element.

6. The admixture of step 5 then may be transferred to a vessel containing an aqueous composition that comprises one or more ascorbate compounds and, in certain systems, one or more gentisate compounds. The mixture may be filtered and transferred to a container such as a syringe, vial or IV bag. Desired dosages can be dispensed for administration to a patient preferably within 5, 4, or 3 days from completing step 5 above.

Pharmaceutical Compositions

In a further aspect, pharmaceutical compositions are provided. Preferred pharmaceutical compositions may include an aqueous composition including 1) a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA and 2) one or more ascorbate compounds. Particularly preferred pharmaceutical compositions may include an aqueous composition including 1) a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA and 2) one or more ascorbate compounds. Preferably, the radiochemical purity of the composition is at least 95%, 96%, 97%, 95% or 99% where the composition is maintained at 30°C or less and for 3, 4 or 5 days or more following preparation of the composition.

In certain preferred embodiments, the pharmaceutical composition is free of unchelated lutetium-177 in an amount of not more than 2, 1.5, 1.0 or 0.5 weight % based on total weight of the pharmaceutical composition, such as may be determined by radiometric detection (including HPLC radiometric detection), where the composition is maintained at 30°C or less and such purity levels are exhibited for 3, 4 or 5 days or more following preparation of the composition.

In additional preferred embodiments, the pharmaceutical composition is free of radiochemical impurities in an amount of not more than 5, 4, 3.5, 3, 2.5, 2, 1.5, 1 or 0.5 weight% based on total weight of the pharmaceutical composition, such as may be determined by radiometric detection (including HPLC radiometric detection), where the composition is maintained at 30°C or less and such purity levels are exhibited for 3, 4 or 5 days or more following preparation of the composition.

In yet still additional preferred embodiments, the pharmaceutical composition is free of chemical impurities in an amount of not more than 5, 4, 3, 2, 1 or 0.5 weight % based on total weight of the pharmaceutical composition, such as may be determined by chromatography or other method including HPLC or HPLC/UV analysis, where the composition is maintained at 30°C or less and such purity levels are exhibited for 3, 4 or 5 days or more following preparation of the composition.

In yet still additional preferred embodiments, the pharmaceutical composition is 1) free of unchelated lutetium-177 in an amount of not more than 2, 1.5, 1.0 or 0.5 weight % (such as may be determined by radiometric detection (including HPLC radiometric detection)); 2) free of radiochemical impurities in an amount of not more than 5, 4, 3.5, 3, 2.5, 2, 1.5, 1 or 0.5 weight% (such as may be determined by radiometric detection (including HPLC radiometric detection); and 3) free of chemical impurities in an amount of not more than 5, 4, 3, 2, 1 or 0.5 weight % (such as may be determined by HPLC/UV analysis), with all weight % based on total weight of the pharmaceutical composition, and where the composition is maintained at 30°C or less and such purity levels are exhibited for 3, 4 or 5 days or more following preparation of the composition.

In certain embodiments, the pharmaceutical composition is formulated for parenteral administration, such as intravenous, intramuscular, intradermal, subcutaneous, intrathecal or intraperitoneal administration. For example, the pharmaceutical composition is formulated for intravenous, intramuscular, subcutaneous or intradermal injection. In preferred aspects, the pharmaceutical composition is formulated for intravenous administration. In typical embodiments, the pharmaceutical composition may be administered in a form of a pharmaceutical aqueous solution.

In certain embodiments, the pharmaceutical composition is an aqueous solution, dispersion or other admixture such as for injection and comprises ^{177}Lu-PSMA I&T (including ^{177}Lu-PSMA I&T having an optical excess of structure 2A) and preferably one or more ascorbate compounds. In further preferred embodiments, the pharmaceutical composition is an aqueous solution, dispersion or other admixture such as for injection and comprises 1) ^{177}Lu-PSMA I&T including ^{177}Lu-PSMA I&T having an optical excess of structure 2A) and preferably one or more ascorbate compounds and one or more gentisate compounds.

In certain preferred embodiments, a pharmaceutical aqueous solution, dispersion or admixture is provided that includes: 1) a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA; and 2) at least one stabilizer compound that preferably can inhibit radiolytic degradation of the composition during storage following preparation of the complex. ^{177}Lu-PSMA I&T is suitably present in a concentration that it provides a volumetric radioactivity of at least 100 MBq/mL, preferably of at least 250, 500, 750 or 1000 MBq/mL within 1, 2, 3, 4 or 5 days following preparation. In certain aspects, ^{177}Lu-PSMA I&T is present in a concentration that it provides a volumetric radioactivity of from 100 to 1000 MBq/mL, preferably from or up to about 250, 500, 750 or 1000 MBq/mL within 1, 2, 3, 4 or 5 days following preparation.

In certain aspects, the one or more stabilizer compounds may be present in a total concentration of at least 5 mg/mL, preferably at least 10 mg/mL of an aqueous pharmaceutical composition.

In certain aspects, the one or more stabilizer compounds are one or more of gentisic acid (2,5-dihydroxybenzoic acid) or salts thereof, ascorbic acid (L-ascorbic acid) or salts thereof (e.g. sodium ascorbate), methionine, histidine, melatonine, N-acetylmethionine, ethanol, or Se-methionine, preferably ascorbic acid or salts thereof and gentisic acid or salts thereof.

In certain aspects, the pharmaceutical aqueous formulation has a shelf life of at least 24 hours at about 30°C or less, at least 48 hours at about 30°C or less, at least 72

hours at 30°C or less, or from 24 hours to 120 hours at 30°C or less, from 24 hours to 96 hours at 30°C or less, from 24 hours to 84 hours at 30°C or less, from 24 hours to 72 hours at 30°C or less, in particular a shelf life of at least 72 hours at 30°C or less. In further particular aspects, the pharmaceutical aqueous formulation has a shelf life of at least 96 hours (or 4 days) at about 30°C or less, or the pharmaceutical aqueous formulation has a shelf life of at least 120 hours (or 5 days) at about 30°C or less, or the pharmaceutical aqueous formulation has a shelf life of at least 144 hours (or 6 days) at about 30°C or less.

In certain aspects, one, two or three total distinct stabilizer compounds are present during the complex formation of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA, preferably in an amount to result in a concentration of from 5 mg/mL or more of the 1-3 stabilizer compounds. As discussed, preferably at least one of the stabilizer compounds will be an ascorbate compound.

In certain aspects, as discussed, one or more stabilizer compounds may be added after formation of the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA, for example upon completion of heating of an admixture of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA. As discussed, preferably at least one of the stabilizer compounds added after formation of ^{177}Lu-PSMA I&T will be an ascorbate compound, for example where such stabilizer compound(s) are added upon temperature reduction/termination at the conclusion of a heating step. In certain aspects, a gentisate compound also will be added after formation of ^{177}Lu-PSMA I&T, for example where such stabilizer compound(s) are added upon temperature reduction/termination at the conclusion of a heating step. As discussed, reduction or termination of temperature or heating can include physical removal of the heating source from the reaction vessel, or termination of power to the heating element.

In certain embodiments, a pharmaceutical aqueous solution may further include a sequestering agent, for example added after formation of a complex lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA, suitably to remove uncomplexed lutetium-177. Suitable sequestering agents may include for example diethylentriaminepentaacetic acid (DTPA) or

a salt thereof, suitably in an amount to result in a concentration of from 0.01 to 0.50 mg/mL of the aqueous ^{177}Lu-PSMA I&T composition.

In a particularly preferred aspect, ^{177}Lu-PSMA I&T is provided as a sterile solution for intravenous use. The ^{177}Lu-PSMA I&T solution suitably may be clear, colorless to slightly yellow. A single-dose vial suitably will contain 6.8 +/- 10% GBq ^{177}Lu-PSMA I&T for example calibrated at 1, 2, 3, 4, 5 or 6 or more days post-day of manufacture in 10 to 14 mL formulated with one or more radioprotectants and may include a buffer. The pH range of the solution is preferably 5.0 to 7.0. As discussed, radioprotectants or stabilizers may be one or more ascorbate compounds and optionally together with one or more gentisate compounds. The ^{177}Lu-PSMA I&T also may be provided in a multi-dose format or packaging, such as a multi-dose vial that contains multiple doses, such as 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more doses of ^{177}Lu-PSMA I&T.

Methods of treatment

As discussed, use of ^{177}Lu-PSMA I&T (including structures 2A and/or 2B above) is provided to treat cancers, including prostate cancer, for example non-metastatic prostate cancer and metastatic prostate cancer, including hormone sensitive prostate cancer, castration resistant prostate cancer (CRPC) and drug-resistant prostate cancer, such as anti-androgen drug (e.g., enzalutamide) resistant prostate cancer.

In such methods, ^{177}Lu-PSMA I&T (including structures 2A and/or 2B above) can be administered to a subject such as a human in an amount effective to treat the cancer (e.g., reduction of tumor size), such as at a dose of about 0.1 GBq to about 30 GBq be suitably administered from a unit dose in a vial or a syringe or as a bulk solution in a vial or a syringe prepared from a cold-kit prepared with lutuetium-177 at a local or central nuclear pharmacy or through cGMP central manufacturing.

In certain embodiments, the subject is suffering from prostate cancer such as one or more of castration-sensitive prostate cancer, castration-resistant prostate cancer, metastatic castration-resistant prostate cancer, advanced stage prostate cancer, drug-resistant prostate cancer such as anti-androgen-resistant prostate cancer (e.g.,

enzalutamide-resistant prostate cancer, abiraterone-resistant prostate cancer, bicalutamide-resistant prostate cancer), docetaxel-resistant prostate cancer, PARP resistant prostate cancer, radium chloride resistant prostate cancer, AR-V7-induced drug-resistant prostate cancer such as AR-V7-induced enzalutamide-resistant prostate cancer, AKR1C3-induced drug-resistant prostate cancer such as AKR1C3-induced enzalutamide-resistant prostate cancer, and combinations thereof.

In particular embodiments, the subject is a human suffering metastatic castration-resistant prostate cancer and an effective amount of ^{177}Lu-PSMA I&T (including ^{177}Lu-PSMA I&T having an optical excess of structure 2A) is administered to the subject to treat the prostate cancer.

In additional particular embodiments, the subject is a human suffering oligometastatic hormone sensitive prostate cancer and an effective amount of ^{177}Lu-PSMA I&T (including ^{177}Lu-PSMA I&T having an optical excess of structure 2A) is administered to the subject to treat the prostate cancer.

In further particular embodiments, the subject is a human suffering metastatic castration-resistant prostate cancer and an effective amount of ^{177}Lu-PSMA I&T including ^{177}Lu-PSMA I&T having an optical excess of structure 2A) is administered to the subject to treat the prostate cancer.

The effective amount of ^{177}Lu-PSMA I&T (including ^{177}Lu-PSMA I&T having an optical excess of structure 2A) radiopharmaceutical administered to a patient will generally be determined by considering the patient record. However, the effective amount suitably may be within a range of about 0.1 GBq to 30 GBq per dose. More specifically, the dose may range from about 1 GBq to about 20 GBq or about 30 GBq per dose subject, for example, about 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 6.8, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, 20, 21.5, 22, 22.5, 23, 23.5, 24, 24.5, 25, 25.5, 26, 26.5, 27, 27.5, 28, 28.5, 29, 29.5 or 30 GBq per dose of ^{177}Lu-PSMA I&T (including ^{177}Lu-PSMA I&T having an optical excess of structure 2A), or any range between two of the above values. The dose can be

administered from a unit dose in a vial or a syringe or as a bulk solution in a vial or a syringe prepared from a cold-kit prepared with lutetium-177 at a local or central nuclear pharmacy or through cGMP central manufacturing.

If necessary or desirable, the treatment may involve more than one administration of an effective amount of ^{177}Lu-PSMA I&T (including ^{177}Lu-PSMA I&T having an optical excess of structure 2A). It is generally beneficial to repeat the administration of ^{177}Lu-PSMA I&T (including ^{177}Lu-PSMA I&T having an optical excess of structure 2A) to the subject after 7 to 56 days, such as at a 4 to 8 week interval.

In a particularly preferred protocol, the ^{177}Lu-PSMA I&T (including ^{177}Lu-PSMA I&T having an optical excess of structure 2A) dosage form is a sterile aqueous solution that is administered by intravenous injection. The dosing regimen may include multiple infusions such as 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 infusions at effective dosages such as of 6.8 GBq +/- 10% each, administered about 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 weeks apart.

Combination therapy

^{177}Lu-PSMA I&T (including structures 2A and/or 2B above) suitably may be administered to a subject in conjunction or combination with one or more other therapeutic agents, particularly one or more other chemotherapeutic agents.

In one aspect, a subject may receive treatment with ^{177}Lu-PSMA I&T (including structures 2A and/or 2B above) in combination with a regime of docetaxel and/or prednisone, particularly for a subject suffering from castration resistant prostate cancer.

In another aspect, a subject may receive treatment with ^{177}Lu-PSMA I&T (including structures 2A and/or 2B above) in combination with a regime that can include chemotherapy such as docetaxel; cisplatin; gemcitabine; cisplatin/gemcitabine; cabazitaxel; one or more antiandrogens such as one or more LHRH agonists, such as leuprolide and goserelin, or antagonists (e.g. firmagon and relugolyx); one or more antiandrogens such as flutamide, nilutamide, bicalutamide, cyproterone, abiraterone, enzalutamide, darolutamide and apalutamide; one or more PARP inhibitors such as olaparib, rucaparib or niraparib, particularly for a subject suffering from prostate cancer including metastatic castration resistant prostate cancer.

In additional aspects, a subject may receive treatment with ^{177}Lu-PSMA I&T (including structures 2A and/or 2B above) in combination with an immunotherapy regime which may include adoptive cell therapies or adoptive immunotherapy.

For example, to treat a patient suffering from cancer, ^{177}Lu-PSMA I&T (including structures 2A and/or 2B above) may be administered in combination with immune effector cells (e.g., T cells, NK cells) engineered to express a Chimeric Antigen Receptor (e.g. CAR T-cell therapy), including to treat a cancer or a disease associated with expression of a tumor antigen.

For a patient suffering from cancer including prostate cancer, ^{177}Lu-PSMA I&T (including structures 2A and/or 2B above) also may be administered in combination with other immune-based therapies such as sipuleucel-T (Provenge) or other immune-boosting approaches including antibody treatments. For instance, in one protocol, ^{177}Lu-PSMA I&T (including structures 2A and/or 2B above) may be administered in combination with one or more monoclonal antibodies such as pembrolizumab (Keytruda), ipilimumab (Yervoy) and/or nivolumab (Opdivo) for treating a patient suffering from cancer, particularly prostate cancer.

As used herein, the term "in combination" in the context of the administration of a therapy to a subject refers to the use of more than one therapy for therapeutic benefit. The term "in combination" in the context of the administration can also refer to the prophylactic use of a therapy to a subject when used with at least one additional therapy. The use of the term "in combination" does not restrict the order in which the therapies (e.g., a first and second therapy) are administered to a subject. A therapy can be administered prior to (e.g., 1 minute, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 1 minute, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapy to a subject in need of treatment as disclosed herein. The therapies are administered to a subject in a sequence and within a time interval such that the therapies can act together. In a particular embodiment, the therapies

are administered to a subject in a sequence and within a time interval such that they provide an increased benefit than if they were administered otherwise. Any additional therapy can be administered in any order with the other additional therapy.

Packaged ^{177}Lu-PSMA I&T and Kits

As discussed above, treatment kits are also provided, including cold kits where the ^{177}Lu-PSMA I&T (including structures 2A and/or 2B above) can be prepared shortly before administration such as in a medical facility, for example a hospital laboratory or nuclear pharmacy. In such a kit, EuK-Sub-kf-iodo-y-DOTAGA may be provided in a vial or other container in lyophilized or other form separate from lutetium-177. The EuK-Sub-kf-iodo-y-DOTAGA and lutetium-177 are reacted as disclosed herein at the medical facility to provide ^{177}Lu-PSMA I&T (including 2A and/or 2B above) which then can be promptly administered to a patient.

In a further aspect, packaged preparations or products of ^{177}Lu-PSMA I&T (including structures 2A and/or 2B above) are also provided. A packaged preparation may comprise 1) ^{177}Lu-PSMA I&T and optionally 2) instructions for using ^{177}Lu-PSMA I&T for treating a cancer such as prostate cancer. Preferably, the packaged preparation will comprise a therapeutically effective amount of ^{177}Lu-PSMA I&T (including structures 2A and/or 2B above).

In certain exemplary packaged preparations or products, ^{177}Lu-PSMA I&T (including structures 2A and/or 2B above) suitably can be packaged in suitable containers labeled, for example, for use as a therapy to treat a subject suffering from prostate cancer. The containers can include ^{177}Lu-PSMA I&T and suitably one or more ascorbate compounds and one or more gentisate compounds as disclosed herein. A product can include a container (e.g., a vial or the like) containing ^{177}Lu-PSMA I&T. In addition, an article of manufacture or kit further may include, for example, packaging materials, instructions for use, syringes, delivery devices, for treating the targeted condition, such as prostate cancer or other cancer.

A packaged system or product may also include a legend (e.g., a printed label or insert or other medium (e.g., an audio or video file) describing the product's use). The legend can be associated with the container (e.g., affixed to the container) and can describe the manner in which the compositions therein should be administered (e.g., the frequency and route of administration), indications therefor, and other uses. The compositions can be ready for administration (e.g., present in dose-appropriate units), and may include one or more additional pharmaceutically acceptable adjuvants, carriers or other diluents.

The following non-limiting examples are illustrative.

Example 1

Radiolabeling was performed using no-carrier added $^{177}LuCl_3$. Radiolabeling was done either directly in the isotope vial, or transferred to a 20 mL vial. ^{177}Lu-PSMA-I&T is prepared as described in Weineisen et al. *J Nucl Med* 2015; 56:1169–1176 by use of racemic EuK-Sub-kf-iodo-y-DOTAGA. ^{177}Lu-PSMA I&T having an optical excess of structure 2A is also prepared as described in Weineisen et al. *J Nucl Med* 2015; 56:1169–1176 using the *S*-isomer of EuK-Sub-kf-iodo-y-DOTAGA (i.e. the compound of structure 1A above). The racemic ^{177}Lu-PSMA-I&T or ^{177}Lu-PSMA I&T having an optical excess of structure 2A was diluted using reaction buffer and was added to a reaction vial to form a Reaction Composition. A thus prepared Reaction Composition was heated with mixing using a shaker at 90 +/- 4 °C. Different reaction times and cool down periods were tested during development, ranging from 10 to 30 minutes of labelling time and 0 to 20 minutes of cool down time. Three different Reaction Compositions ((A), (B) and (C) set forth below) were assessed.

The formulated racemic ^{177}Lu-PSMA-I&T and ^{177}Lu-PSMA I&T having an optical excess of structure 2A batches were sampled for quality control testing and tested for stability for up to 6 days post-day of manufacture. Batches of both 1) racemic ^{177}Lu-PSMA-I&T and 2) ^{177}Lu-PSMA I&T having an optical excess of structure 2A at room temperature (25°C) and 2-8 °C storage were evaluated during development. Reverse-

phase HPLC with radiometric and UV detection and thin layer chromatography with radiometric detection were used to assess chemical and radiochemical impurities.

(1) Reaction Buffer Compositions evaluated:

(A) 99 to 247 mg/mL Ascorbate (pH 4.5 to 6), made from sodium L-ascorbate and ascorbic acid (preferred condition 162 mg/mL, pH 5.5 to 6.0)

(B) 5.1 to 12.5 mg/mL Gentisic Acid (0.4 M acetate used as buffer, pH 5 – 6.5), made from gentisic acid

(C) 100 mg/mL Ascorbate with 5.0 mg/mL Gentisic Acid (pH 5 – 6.5), made from sodium L-ascorbate, ascorbic acid and gentisic acid

(D) Reaction Buffer Compositions were diluted 1.48:1 – 0.4 N HCl:Reaction buffer

(2) Formulation Buffer Compositions evaluated:

(A) 65 to 68 mg/mL Ascorbate with 25 to 28 mg/mL Gentisic Acid (pH 6 - 7), made from sodium L-ascorbate and gentisic acid (preferred condition)

(B) 64 to 86 mg/mL Ascorbate (pH 6 - 7), made from sodium L-ascorbate

(C) Formulation Buffer Compositions were diluted 11.5:1 – Formulation Buffer:Reaction Composition

The conditions as set forth in the following Table 1 were evaluated:

Table 1:

	Reaction Compositions				Formulation Compositions		
	Gentisic Acid	Ascorbate	Acetate (buffer)	Reaction Time (Min)	Gentisic Acid	Ascorbate	Radioactivity Concentration at Activity Reference Time
Experiment 1	+	-	+	30	-	+	0.93
Experiment 2	+	-	+	30	-	+	0.97

Experiment 3a	+	-	+	20	-	+	0.53
Experiment 3b	+	-	+	20	+	+	0.48
Experiment 3c	+	+	-	20	-	+	0.58
Experiment 3d	+	+	-	20	+	+	0.56
Experiment 4a	-	+	-	20	+	+	0.49
Experiment 4b	-	+	-	20	+	+	0.49
Experiment 4c	+	+	-	20	+	+	0.49
Experiment 4d	+	+	-	20	+	+	0.49
Experiment 5a	+	-	+	20	+	+	0.49
Experiment 5b	-	+	-	20	+	+	0.49
Experiment 6a	+	-	+	20	+	+	0.49
Experiment 6b	-	+	-	20	+	+	0.49
Experiment 7	-	+	-	20	+	+	0.49
Experiment 8	-	+	-	15	+	+	0.49
Experiment 9	-	+	-	10	+	+	0.49
Experiment 10	-	+	-	10	+	+	0.49
Experiment 11	-	+	-	10	+	+	0.49
Experiment 12	-	+	-	10	+	+	0.49

In each of Examples 1, 2, 3a, 3b, 3c, 3d, 4a, 4b, 4c and 4d, racemic EuK-Sub-kf-iodo-y-DOTAGA and racemic ^{177}Lu-PSMA I&T was used. In each of Examples 5a, 5b, 6a, 6b, 7, 8, 9, 10, 11 and 12 *S*-isomer enriched EuK-Sub-kf-iodo-y-DOTAGA (1A above) and ^{177}Lu-PSMA I&T having an optical excess of structure 2A were used. Results:

1. Lu-177 Incorporation:

Chromatography shows the amount of Lu-177 incorporated into the EuK-Sub-kf-iodo-y-DOTAGA was >99.5% for all reactions at completion of production. This demonstrates that under all conditions, including a reaction time limited to 10 minutes, full incorporation of Lu-177 into EuK-Sub-kf-iodo-y-DOTAGA was achieved. The ability to incorporate Lu-177 in a reduced time, reduced the number of impurities at the end of production.

2. Negative Impact of Gentisic Acid in the Reaction Composition (incorporation reaction):

In each of Experiments 1 and 2, gentisic acid was present in the Reaction Composition, but the amount of gentisic acid present in the Reaction Composition was double in Example 2 relative to Example 1. Specifically, in Experiment 1, 2.5 mg/mL of gentisic acid was used in the Reaction Composition; and in Experiment 2, 5.0 mg/mL of gentisic acid was used in the Reaction Composition. Over the 5 or 6 day evaluation period, it was found that radiochemical purity dropped 5% for the Experiment 1 sample and radiochemical purity dropped 13% for the Experiment 2 sample.

Experiments 3 through 6 demonstrated that the inclusion of only gentisic acid in the reaction results in an impurity peak that elutes at ~10.2 min; this peak is absent when only ascorbate is used. When gentisic acid and ascorbate are both used in the reaction, the peak at ~10.2 min also may be present (see FIGS. 1A-1D) in certain instances. Therefore, to minimize impurities, gentisic acid may be excluded from the incorporation reaction.

3. HPLC verification

In FIG. 1A, HPLC shows an incorporation reaction with acetate and gentisic acid (peak at 10.2 min always appears): 20 min reactions at 90°C. In FIGS. 1B-1C, HPLC shows reactions with gentisic acid and ascorbate (peak at 10.2 min appears sometimes): 20 min reactions at 90 °C. In FIG. 1D, HPLC shows reaction with just ascorbate (peak at ~10.2 min never appears): 20 min reactions at 90°C.

4. Positive Impact of Gentisic Acid in the Formulation Composition

It was found that inclusion of gentisic acid in the Formulation Composition at the time of or following termination of the reaction incorporating Lu-177 with EuK-Sub-kf-iodo-y-DOTAGA favorably impacted radiochemical purity of the racemic ^{177}Lu-PSMA-I&T or ^{177}Lu-PSMA I&T having an optical excess of structure 2A. That is, inclusion of gentisic acid in the Formulation Composition showed a reduced drop in radiochemical purity over time. Thus, over the 5 or 6 day evaluation period, in Experiment 3c where gentisic acid was not present in the Formulation Composition, radiochemical purity dropped 10.2%, whereas in Experiment 3d where gentisic acid was present in the Formulation Composition, radiochemical purity dropped 7.6%.

Example 2

Further evaluations were conducted as follows. In Table 2, Conditions 1-8 that are not reported in Example 1 are indicated by bold text. Experiments 1, 2, 3a-3d, 4a-4d, 5a-5b and 6a,6b in Table 2 below that are also disclosed in Example 1 above are without bold text in Table 2 below.

Radiolabeling was performed using no-carrier added $^{177}LuCl_3$. Radiolabeling was done either directly in the isotope vial, or transferred to a 20 mL vial. ^{177}Lu-PSMA-I&T is prepared as described herein and in Weineisen et al. *J Nucl Med* 2015; 56:1169–117 by use of racemic EuK-Sub-kf-iodo-y-DOTAGA. ^{177}Lu-PSMA I&T having an optical excess of structure 2A is also prepared as described in Weineisen et al. *J Nucl Med* 2015; 56:1169–1176 using the *S*-isomer of EuK-Sub-kf-iodo-y-DOTAGA (i.e. the compound of structure 1A above). ^{177}Lu-PSMA-I&T is also commercially available. The racemic ^{177}Lu-PSMA-I&T or ^{177}Lu-PSMA I&T having an optical excess of structure 2A was diluted using reaction buffer and was added to a reaction vial to form a Reaction Composition. A thus prepared Reaction Composition was heated as per the method followed. Different reaction times were tested during development, ranging from 10 to 30 mins of labelling time. Three different Reaction Compositions ((A), (B) and (C) set forth below) were assessed.

The formulated racemic ^{177}Lu-PSMA-I&T and ^{177}Lu-PSMA I&T having an optical excess of structure 2A batches were sampled for quality control testing and tested for stability for up to 6 days post-day of manufacture. Batches of both racemic ^{177}Lu-PSMA-I&T and ^{177}Lu-PSMA I&T having an optical excess of structure 2A at room temperature (25°C) and 2-8 °C storage were evaluated during development. Reverse-phase HPLC with radiometric and UV detection and thin layer chromatography with radiometric detection were used to assess chemical and radiochemical impurities.

(3) Reaction Compositions evaluated at precursor amounts of 125 to 250 µg:

(A) 40 to 100 mg/mL Ascorbate (pH 4.5 to 6), made from sodium L-ascorbate and ascorbic acid (preferred condition 65 mg/mL, pH 5.5 to 6.0)

(B) 2.0 to 9.8 mg/mL Gentisic Acid (27 to 35 mg/mL acetate used as buffer, pH 5 – 6.5), made from Gentisic acid (pH 5-6.5)

(C) 40 mg/mL Ascorbate with 2.0 to 2.1 mg/mL Gentisic Acid, made from sodium L-ascorbate, ascorbic acid and gentisic acid

(4) Formulation Compositions evaluated:

(A) 1 mg/mL Gentistic Acid (27 to 35 mg/mL acetate used as a buffer, pH 5.5), made from Gentisic acid

(B) 59 to 79 mg/mL Ascorbate with 0.16 to 26 mg/mL Gentisic Acid (pH 6 - 7), made from sodium L-ascorbate and gentisic acid (preferred condition)

The conditions as set forth in the following Table 2 were evaluated:

Table 2:

Reference	Reaction Compositions				Formulation Compositions (with ^{177}Lu-PSMA-I&T)		Isomer	
	Gentisic Acid (mg/mL)	Ascorbate (mg/mL)	Buffer	Reaction Time (Min) / Temp (°C	Gentisic Acid (mg/mL)	Sodium Ascorbate (mg/mL)		RAC [2]
Condition 1	0	0	MES[1]	20 / 95	0	0	S-isomer	0.81
Condition 2	3.3	0	Sodium Acetate	30 / 90	1	0	S-isomer	0.74

Condition 3	0	0	Sodium Acetate	30 / 90	1	0	S-isomer	0.74
Condition 4	9.8	0	Sodium Acetate	20 / 90	25	58	S-isomer	0.79
Condition 5	0	65	none	10 / 90	26	66	S-isomer	
Condition 6	0	80	none	10 / 80	26	66	S-isomer	0.47
Condition 7	0	80	none	10 / 70	26	66	S-isomer	0.47
Condition 8	0	80	none	10 / 60	26	66	S-isomer	0.47
Experiment 1	2.5	0	Sodium Acetate	30 / 90	0.20	59	racemic	0.93
Experiment 2	5.0	0	Sodium Acetate	30 / 90	0.40	68	racemic	0.97
Experiment 3a	2.1	0	Sodium Acetate	20 / 90	0.16	79	racemic	0.53
Experiment 3b	2.1	0	Sodium Acetate	20 / 90	24	59	racemic	0.48
Experiment 3c	2.1	40	none	20 / 90	0.16	82	racemic	0.58
Experiment 3d	2.1	40	none	20 / 90	24	62	racemic	0.56
Experiment 4a	0	40	none	20 / 90	23	62	racemic	0.49
Experiment 4b	0	40	none	20 / 90	26	62	racemic	0.49 [1/2 RAC]
Experiment 4c	2.0	40	none	20 / 90	23	62	racemic	0.49 [1/2 RAC]
Experiment 4d	2.0	40	none	20 / 90	26	62	racemic	0.49
Experiment 5a	3.3	0	Sodium Acetate	20 / 90	23	62	S-isomer	0.49
Experiment 5b	0	65	none	20 / 90	23	64	S-isomer	0.49
Experiment 6a	0	0	none	20 / 90	23	62	S-isomer	0.49
Experiment 6b	0	100	none	20 / 90	23	63	S-isomer	0.49
Experiment 7	0	65	none	20 / 90	23	63	S-isomer	0.49
Experiment 8	0	65	none	15 / 90	26	66	S-isomer	0.49
Experiment 9	0	65	none	10 / 90	26	66	S-isomer	0.49

(1) MES = 2-(N-morpholino)ethanesulfonic acid
(2) RAC = Radioactivity Concentration at Activity Reference Time

Results:

1. Incorporation Reaction and Formulation Compositions for Condition 1, 2 and 3 in Table 2

Radiolabeling was performed using no-carrier added $^{177}LuCl_3$ following the radiolabeling conditions described by Weineisen et al. *J Nucl Med* 2015; 56:1169–1176 and Chatalic et al. *Theranositcs* 2016; 6:849-861 (Chatalic) for the preparation of ^{177}Lu-PSMA-I&T for pre-clinical or clinical use. Thin layer chromatography shows the amount of Lu-177 incorporated into the EuK-Sub-kf-iodo-y-DOTAGA was >99.5% for all reactions at completion of production at reaction temperatures of 95°C and 90°C for 20 and 30 minutes. The conditions are described in Table 2 above.

Batches of both racemic ^{177}Lu-PSMA-I&T and ^{177}Lu-PSMA I&T having an optical excess of structure 2A at room temperature (25°C) and 2-8°C storage were evaluated during development. Reverse-phase HPLC with radiometric and UV detection and thin layer chromatography with radiometric detection were used to assess chemical and radiochemical impurities.

HPLC showed that radiochemical purity was 96.7% for Condition 2, 87.4% for Condition 3 and 87.4% for Condition 1 post-formulation. After two days, the radiochemical purity was 78.3% for Condition 2, 70.7% for Condition 3 and 27% for Condition 1 at room temperature, respectively. After six days, the radiochemical purity was 58.0% for Condition 2, 55.6% for Condition 3 and 4.3% for Condition 1 at room temperature, respectively. These results demonstrate that the preparation of ^{177}Lu-PSMA-I&T under such conditions requires heating above 90°C for greater than 20 minutes, the incorporation conditions yield a product with radiochemical purity <97% at the time of formulation and a rapid drop in radiochemical purity over time is observed and is related to the formation of a greater number of ^{177}Lu-PSMA-I&T related impurities.

2. Incorporation Reaction and Formulation Compositions

The following procedures were utilized for Conditions 4-8 and Experiments 1, 3a-3d, 4a-4d, 5a-5b and 6a,6b with radiolabeling was performed using no-carrier added $^{177}LuCl_3$ following the radiolabeling conditions set forth in Table 2 above. Thin layer chromatography or HPLC shows the amount of Lu-177 incorporated into the EuK-Sub-kf-iodo-y-DOTAGA was >99.5% for all reactions at completion of production at reaction temperatures of 90°C for 30 minutes, and surprising for as short 10 min at only 60°C. HPLC showed that radiochemical purity was 99.2% post incorporation reaction for Condition 4 and the radiochemical purity for Condition 2 was 99.4% post incorporation reaction. After two days the radiochemical purity for Condition 4 is 99.1% at room temperature and after two days the radiochemical purity for Condition 5 is 99.2% at room temperature. After six days the radiochemical purity for Condition 4 is 97.6% at room temperature and Condition 5 is 96.9% at room temperature. The preparation of ^{177}Lu-PSMA-I&T following the conditions described in Condition 4 and Condition 5, demonstrates for the first time a product that is >99% pure post incorporation reaction and maintains >95% radiochemical purity over 6 days at room temperature in the Formulation Composition. In addition, ^{177}Lu-PSMA-I&T was formed under milder conditions (60°C) for as little as 10 minutes.

3. Negative Impact of Gentisic Acid on product purity and stability when included in the Reaction Composition (incorporation reaction):

In FIG. 1A (Experiment 3a), the HPLC chromatogram shown for an incorporation reaction with acetate and gentisic acid has a peak at 10.2 min that is consistent with a gentisate adduct impurity. The same peak is found in the HPLC chromatograms for Condition 4, Experiments 1, 2, 3a, 3b, 3c,, 3d, 5a, 6a and Condition 2. In FIGS. 1B-1C (Experiment 3c and 4d), the HPLC chromatograms show an incorporation reaction with gentisic acid and ascorbate where the gentisate adduct impurity is not consistently formed, i.e. the peak at 10.2 min, even through gentisate is present. This inconsistency in the formation the gentisate adduct impurity is consistent with the results of Experiments 3d and 4c. In FIG. 1D (Experiment 4a), the HPLC chromatogram shown for an incorporation

reaction with just ascorbate the gentisate adduct impurity is not formed, i.e. the peak at 10.2 min is absent. The same result, i.e. lack of the gentisate adduct impurity, was also found for Conditions 5, 7 and 8, Experiments 4a, 4b, 5b, 6b, 7, 8, 9, 10, 11 and 12 where only ascorbate was present in the incorporation reaction. In FIG. 1E and 1F (Condition 3 and Condition 1 respectively), the HPLC chromatogram shown for an incorporation reaction with acetate or 2-(N-morpholino)ethanesulfonic acid that does not have a peak at 10.2 min.

Therefore, to minimize impurities, gentisic acid may be excluded from the incorporation reaction.

To maintain high radiochemical purity during the incorporation reaction and during storage, ascorbate must be included in the incorporation reaction.

4. Positive Impact of Gentisic Acid in the Formulation Composition

It was found that inclusion of gentisic acid in combination with an ascorbate compound in the Formulation Composition at the time of or following termination of the reaction incorporating Lu-177 with EuK-Sub-kf-iodo-y-DOTAGA favorably impacted radiochemical purity of the racemic ^{177}Lu-PSMA-I&T or ^{177}Lu-PSMA I&T having an optical excess of structure 2A. That is, inclusion of gentisic acid in the Formulation Composition showed a reduced drop in radiochemical purity over time with out the formation of the gentisate adduct impurity (see FIG. 1D, which is consistent with Conditions 5, 7 and 8, Experiments 4a, 4b, 5b, 6a, 6b, 7, 8 and 12). Thus, over the 5 or 6 day evaluation period, in Experiment 3c where gentisic acid was not present in the Formulation Composition, radiochemical purity dropped 10.2%, whereas in Experiment 3d where gentisic acid was present in the Formulation Composition, radiochemical purity dropped 7.6%.

Example 3

The following is a preferred preparation process as also generally depicted schematically in FIG. 2.

(1) Prepare all solutions

a. Reaction Buffer prepared by combining sodium L-ascorbate and ascorbic acid to yield approximately 162 mg/mL Ascorbate (pH 5.5 – 6).
b. Formulation Buffer prepared by combining sodium L-ascorbate and gentisic acid to yield approximately 66 mg/mL Sodium Ascorbate with approximately 28 mg/mL Gentisic acid (pH 6 - 7).
c. 0.04 N HCl

(2) Using Reaction Buffer, dissolve 250 ug of precursor (i.e. racemic EuK-Sub-kf-iodo-y-DOTAGA or *R*-isomer of EuK-Sub-kf-iodo-y-DOTAGA (compound of formula 1A)) to approximately 424 µg/mL (Precursor Solution).

(3) Add additional 0.04N HCl to the lutetium-177 vial (Reaction vial) in order to achieve a radioactive concentration of 7.8 GBq/mL).

(4) Add sufficient quantity of the Precursor Solution to the lutetium-177 vial (Reaction vial) containing no-carrier added lutetium-177 in 0.4 N HCl

(5) Heat vial containing the Reaction Composition in an aluminum block with heating at 90 +/- 4°C and shaking at 300 rpm for 10 +/- 1 min.

(6) Add Formulation Buffer into vial (Formulation vial) and mix the Reaction vial to ensure homogeneity of the contents.

(7) Sterile filter diluted ^{177}Lu-PSMA-I&T (through 2 x 0.22 µm filters) into a vial or IV bag.

(8) Rinse Reaction Vial with a sufficient quantity of and sterile filter rinse (through 2 x 0.22 µm filters) into a vial or IV bag with the diluted 177Lu-PSMA-I&T.

(9) Add further Formulation Buffer to yield final bulk drug product in the Formulation Composition.

(10) Dispense fixed volume doses calibrated to a suitable number of days post-manufacturing.

The above process also can be utilized to prepare ^{177}Lu-PSMA I&T that is substantially optically enriched with or is an enantiomerically pure mixture of the *R*-isomer of ^{177}Lu-PSMA I&T (compound of structure 2B above) by use of the *R*-isomer of EuK-Sub-kf-iodo-y-DOTAGA (compound of structure 1B)).

Example 4: Treatment protocol

A human male patient is selected for treatment after being diagnosed with metastatic castration-resistant prostate cancer (such as manifested by progression of the disease despite surgical or chemical castration) who have progressed following treatment first line androgen receptor-axis-targeted (ARAT) therapies.

^{177}Lu-PSMA I&T having an optical excess of structure 2A in a sterile aqueous solution is administered by intravenous injection. The dosing regimen may include four infusions of 6.8 GBq +/- 10% each, administered 8 weeks apart.

Incorporation by reference

The entire contents of all patents, published patent applications and other disclosures cited herein are hereby expressly incorporated herein in their entireties by reference.

What is claimed is:

1. A pharmaceutical composition comprising:

(a) a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA;

(b) one or more ascorbate compounds.

2. The composition of claim 1 wherein the composition is free of a gentisate adduct impurity.

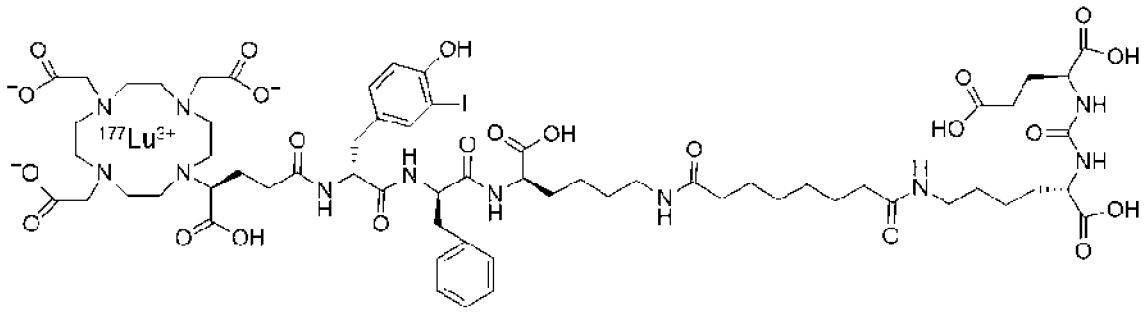
3. The composition of claim 1 or 2 wherein the composition comprises one or more stabilizers in addition to one or more ascorbate compounds.

4. The composition of any one of claims 1 through 3 wherein the composition at least substantially free of a gentisate compound.

5. The composition of any one of claims 1 through 3 wherein the composition comprises one or more gentisate compounds.

6. The composition of any one of claims 1 through 5 wherein the composition is an aqueous formulation.

7. The composition of any one of claims 1 through 6 wherein the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA has the following structure:



8. The composition of any one of claims 1 through 7 wherein the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is:

1) free of unchelated lutetium-177 in an amount of 1 weight % or less; and/or

2) free of radiochemical impurities in an amount of 3 weight % or less; and/or

3) free of chemical impurities in an amount of 5 weight % or less,

all weight % based on total weight of the ^{177}Lu-PSMA I&T, and

where complex is maintained at 30°C or less and such purity levels are exhibited for 3 days or more following preparation of the complex.

9. A pharmaceutical composition comprising:

(a) a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA;

(b) one or more stabilizer compounds,

wherein the composition at least substantially free of a gentisate compound.

10. A pharmaceutical composition comprising:

(a) a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA;

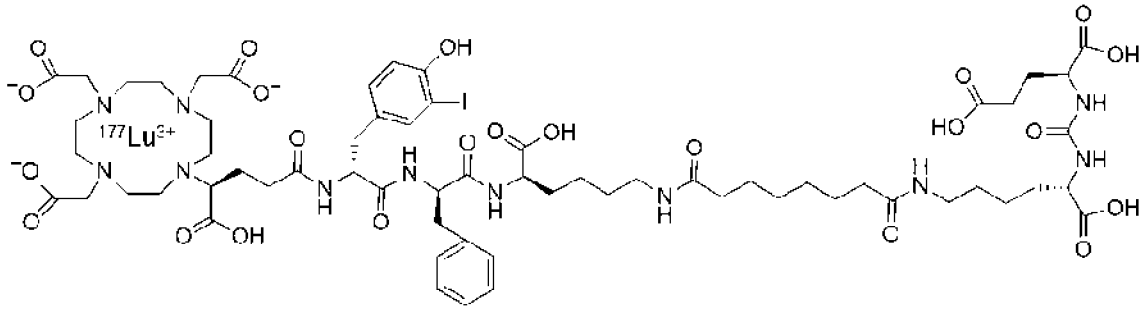
(b) one or more stabilizer compounds,

wherein the composition at least substantially free of a gentisate acid adduct impurity.

11. The composition of claim 9 or 10 wherein the composition comprises one or more stabilizers in addition to one or more ascorbate compounds.

12. The composition of any one of claims 9 through 11 wherein the composition is an aqueous formulation.

13. The composition of any one of claims 9 through 12 wherein the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA has the following structure:



14. The composition of any one of claims 9 through 13 wherein the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is:

1) free of unchelated lutetium-177 in an amount of 1 weight % or less; and/or

2) free of radiochemical impurities in an amount of 3 weight % or less; and/or

3) free of chemical impurities in an amount of 5 weight % or less,

all weight % based on total weight of the ^{177}Lu-PSMA I&T, and

where complex is maintained at 30°C or less and such purity levels are exhibited for 3 days or more following preparation of the complex.

15. A method for preparing ^{177}Lu-PSMA I&T, comprising:

a) admixing 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA in the substantial or complete absence of a gentisate compound;

b) heating the admixed 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA in the substantial or complete absence of a gentisate compound,

wherein a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is formed.

16. A method for treating a patient suffering from cancer, comprising:

a) admixing 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA in the substantial or complete absence of a gentisate compound;

b) heating the admixed 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA in the substantial or complete absence of a gentisate compound, wherein a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is formed; and

c) administering the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA to patient.

17. The method of claim 16 wherein the subject is suffering from prostate cancer.

18. The method of any one of claims 15 through 17 wherein 1) lutetium-177, 2) EuK-Sub-kf-iodo-y-DOTAGA and 3) one or more stabilizer compounds are admixed in the absence of a gentisate compound.

19. The method of any one of claims 15 through 18 wherein 1) lutetium-177, 2) EuK-Sub-kf-iodo-y-DOTAGA and 3) one or more stabilizer compounds are heated in the absence of a gentisate compound.

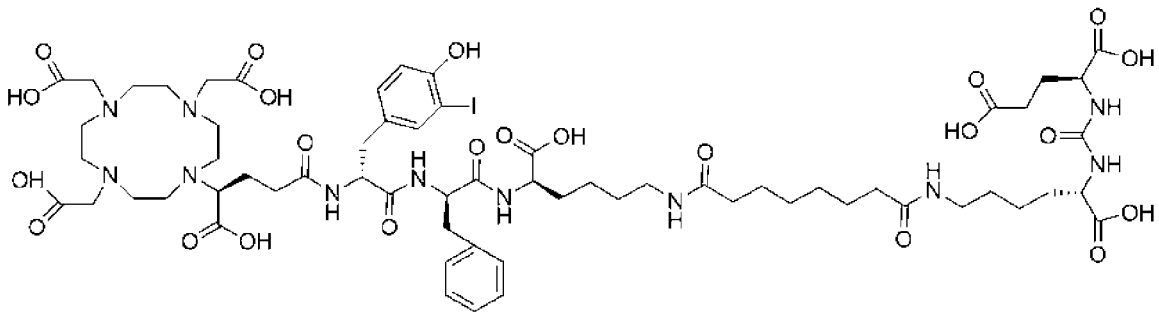
20. The method of any one of claims 15 through 19 wherein one or more ascorbate compounds are admixed with 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA.

21. The method of any one of claims 15 through 20 further comprising adding one or more ascorbate compounds to the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA.

22. The method of any one of claims 15 through 21 further comprising adding one or more gentisate compounds to the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA.

23. The method of claim 22 wherein the one more gentisate compounds are added while or after heating is reduced or terminated.

24. The method of any one of claims 15 through 23 wherein the EuK-Sub-kf-iodo-y-DOTAGA has in optical excess the following structure 1A:



1A

25. The method of any one of claims 15 through 24 wherein the EuK-Sub-kf-iodo-y-DOTAGA is a racemic mixture.

26. The method of any one of claims 15 through 25 wherein the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA does not contain an impurity having a relative retention time of approximately of 9 to 12 minutes by high-performance liquid chromatography.

27. The method of any one of claims 15 through 26 wherein the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is:

1) free of unchelated lutetium-177 in an amount of 1 weight % or less; and/or

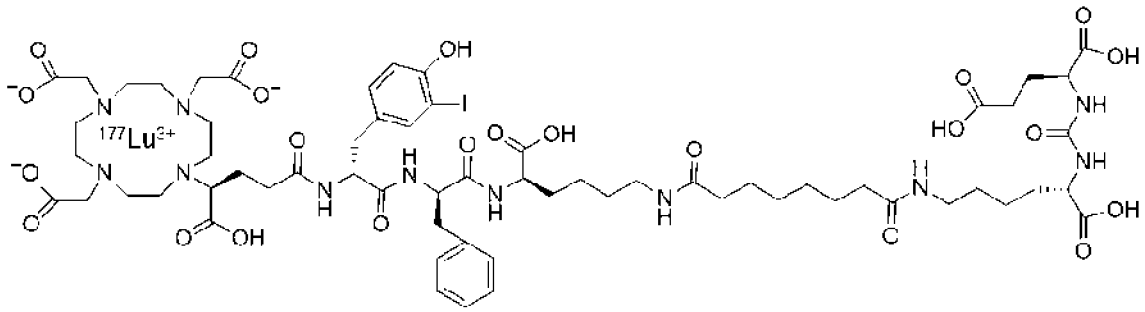
2) free of radiochemical impurities in an amount of 3 weight % or less; and/or

3) free of chemical impurities in an amount of 5 weight % or less,

all weight % based on total weight of the ^{177}Lu-PSMA I&T, and

where complex is maintained at 30°C or less and such purity levels are exhibited for 3 days or more following preparation of the complex.

28. The method of any one of claims 15 through 27 wherein the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA has the following structure:



29. A method for preparing ^{177}Lu-PSMA I&T, comprising:

a) admixing 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA;

b) heating the admixed 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA, wherein a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is formed; and

c) adding or more ascorbate compounds to the formed complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA while or after the heating is reduced or terminated.

30. A method treating a patient suffering from cancer, comprising:

a) admixing 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA;

b) heating the admixed 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA, wherein a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is formed;

c) adding or more ascorbate compounds to the formed complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA while or after the heating is reduced or terminated; and

. d) administering the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA to patient.

31. The method of claim 30 wherein the subject is suffering from prostate cancer.

32. The method of claim 30 or 31 wherein one or more ascorbate compounds are admixed with 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA.

33. A method for preparing ^{177}Lu-PSMA I&T, comprising:

a) admixing 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA;

b) heating the admixed 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA for 15 minutes or less;

wherein a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is formed.

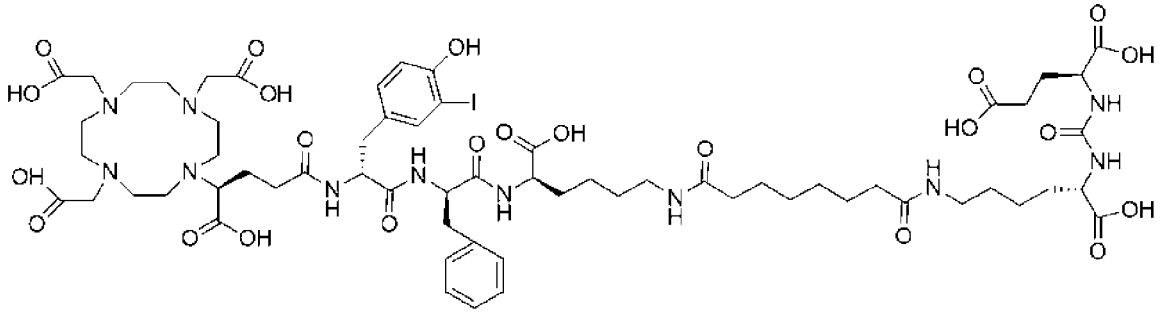
34. A method for preparing ^{177}Lu-PSMA I&T, comprising:

a) admixing 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA;

b) heating the admixed 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA for 15 minutes or less, wherein a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is formed; and

c) administering the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA to patient.

35. The method of claim 33 or 34 wherein the EuK-Sub-kf-iodo-y-DOTAGA has in substantial optical excess the following stereoisomer of structure 1A:



1A

36. The method of claim 33 or 34 wherein the EuK-Sub-kf-iodo-y-DOTAGA is a racemic mixture.

37. The method of any one of claims 33 through 36 wherein one or more ascorbate compounds are admixed with 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA.

38. The method of any one of claims 33 through 37 wherein the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA does not contain an impurity having a relative retention time of approximately of 9 to 12 minutes by high-performance liquid chromatography.

39. The method of any one of claims 33 through 38 wherein the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA does not contain a gentisate adduct impurity.

40. The method of any one of claims 33 through 39 wherein the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is:

1) free of unchelated lutetium-177 in an amount of 1 weight % or less; and/or

2) free of radiochemical impurities in an amount of 3 weight % or less; and/or

3) free of chemical impurities in an amount of 5 weight % or less,

all weight % based on total weight of the ^{177}Lu-PSMA I&T, and

where complex is maintained at 30°C or less and such purity levels are exhibited for 3 days or more following preparation of the complex.

41. The method of any one of claims 33 through 40 wherein the admixture is heated at a temperature not exceeding about 94°C.

42. The method of any one of claims 33 through 41 wherein incorporation of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is greater than 98 mole percent.

43. The method of any one of claims 33 through 42 wherein the admixed 1) lutetium-177 and 2) EuK-Sub-kf-iodo-y-DOTAGA during heating is at least substantially free of a gentisate compound.

44. The method of any one of claims 33 through 43 further comprising adding one or more ascorbate compounds to the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA.

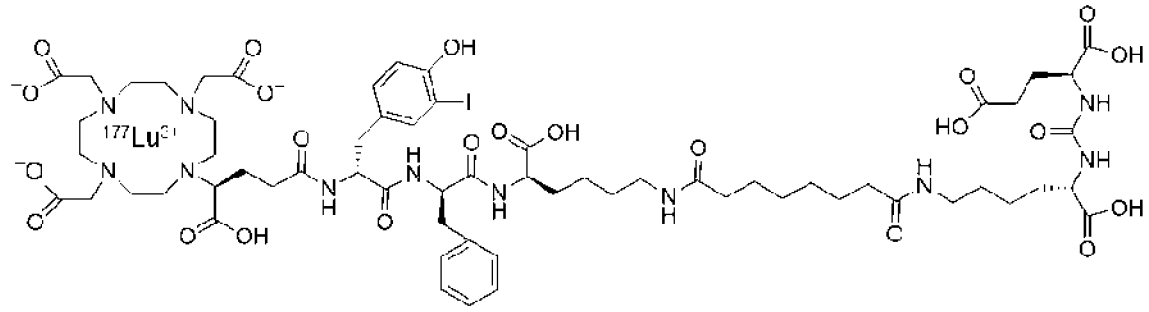
45. The method of any one of claims 34 through 43 wherein prior to the administering one or more ascorbate compounds are added to the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA.

46. The method of claim 44 or 45 wherein the one more ascorbate compounds are added while or after heating is reduced or terminated.

47. The method of any one of claims 33 through 46 further comprising adding one or more gentisate compounds to the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA.

48. The method of claim 47 wherein the one more gentisate compounds are added while or after heating is reduced or terminated.

49. The method of any one of claims 33 through 48 wherein the complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA has the following structure:



50. A complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA obtainable by a method of any one of claims 15 through 49.

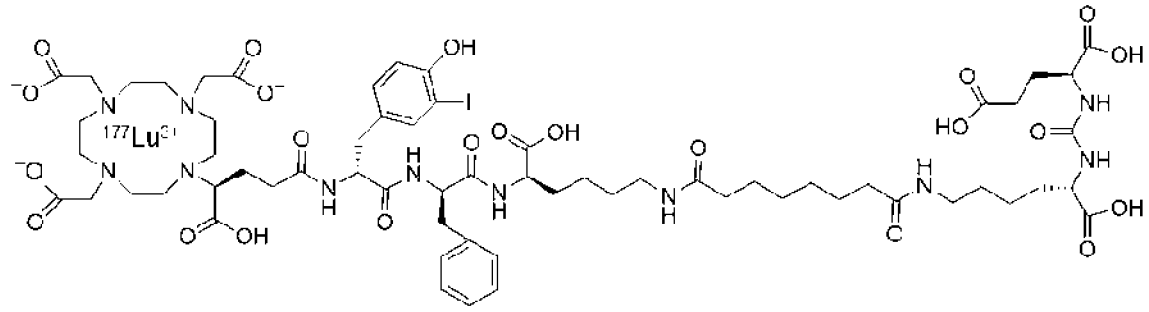
51. A complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA obtained by a method of any one of claims 15 through 49.

52. A complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA, wherein the complex is free of an impurity having a retention time of approximately of 9 to 12 minutes by high-performance liquid chromatography.

53. A complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA, wherein the complex is free of a gentisate adduct impurity.

54. A pharmaceutical composition comprising a complex of any one of claims 50 through 53.

55. The pharmaceutical composition of claim 54 wherein the complex has the following structure:



56. The pharmaceutical composition of claim 54 or 55 wherein the composition is an aqueous formulation.

57. The pharmaceutical composition of any one of claims 54 through 56 wherein the composition comprises one or more stabilizer compounds.

58. The pharmaceutical composition of any one of claims 54 through 57 wherein the composition comprises one or more ascorbate compounds.

59. The pharmaceutical composition of any one of claims 54 through 58 wherein the composition is free of a gentisate adduct impurity.

60. The pharmaceutical composition of any one of claims 54 through 59 wherein the composition is free of a gentisate compound.

61. A pharmaceutical composition or complex of any one of claims 1 through 14 or 50 through 60 wherein a complex of lutetium-177 and EuK-Sub-kf-iodo-y-DOTAGA is present in substantial optical excess.

62. A method of treating a subject suffering from cancer, comprising administering to the subject an effective amount of a composition or complex of any one of any one of claims 1 through 14 or 50 through 61.

63. The method of claim 62 wherein the subject is suffering from prostate cancer.

FIG. 1A
Auto-Scaled Chromatogram

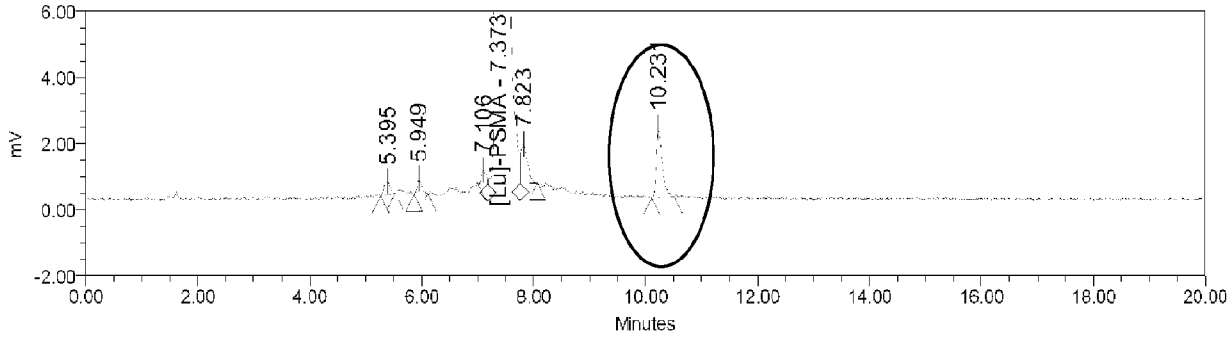


FIG. 1B
Auto-Scaled Chromatogram

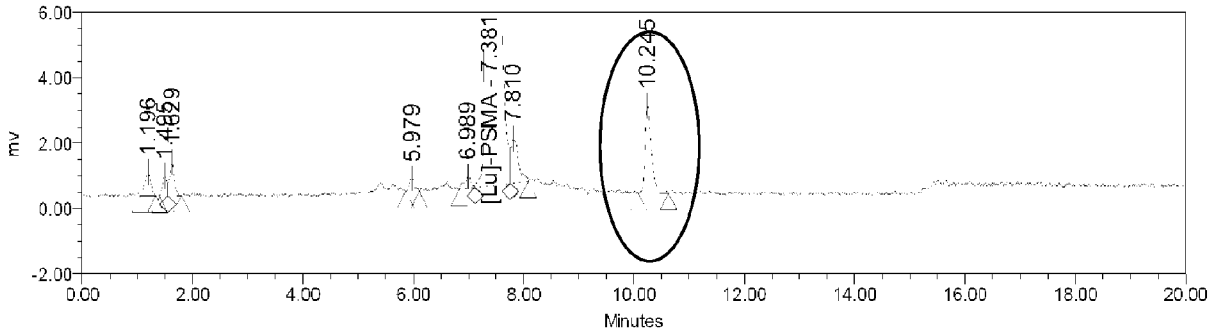


FIG. 1C
Auto-Scaled Chromatogram

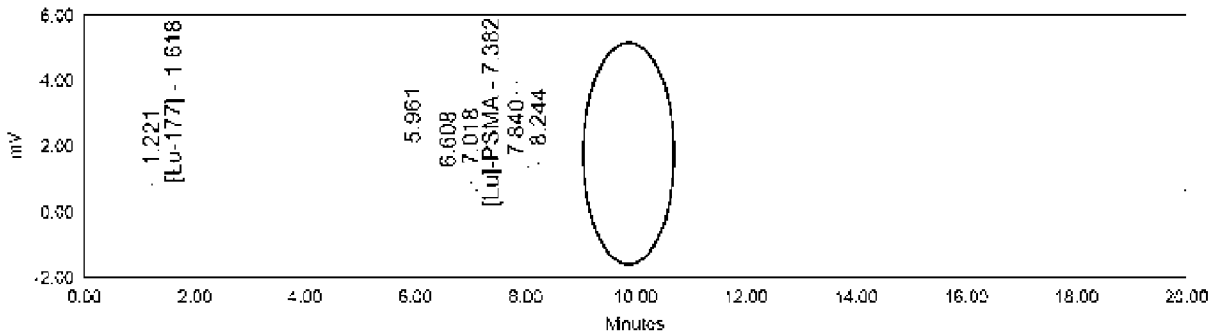


FIG. 1D
Auto-Scaled Chromatogram

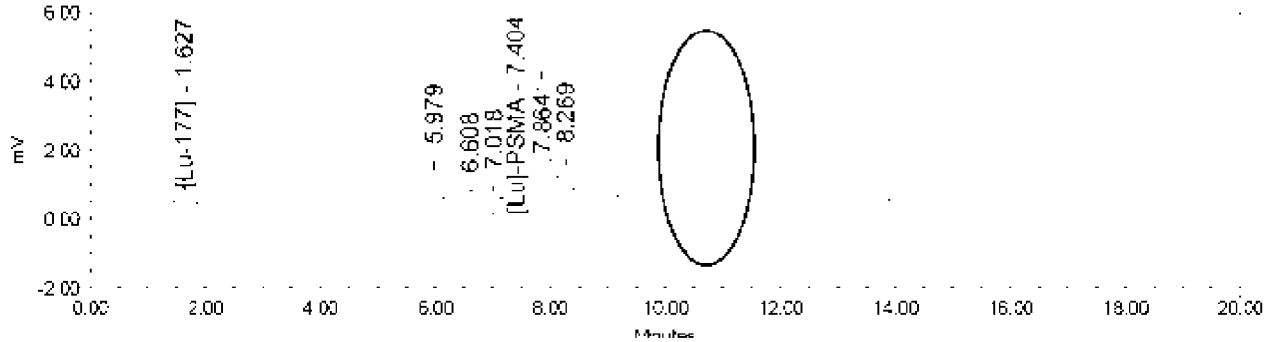


FIG. 1E
Auto-Scaled Chromatogram

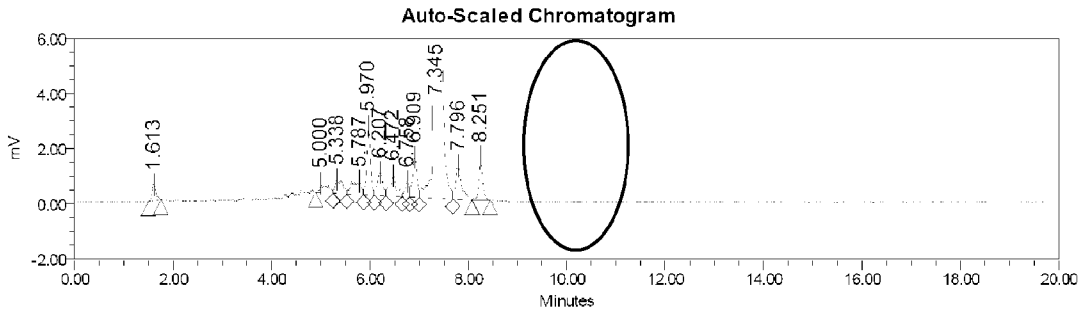


FIG. 1F
Auto-Scaled Chromatogram

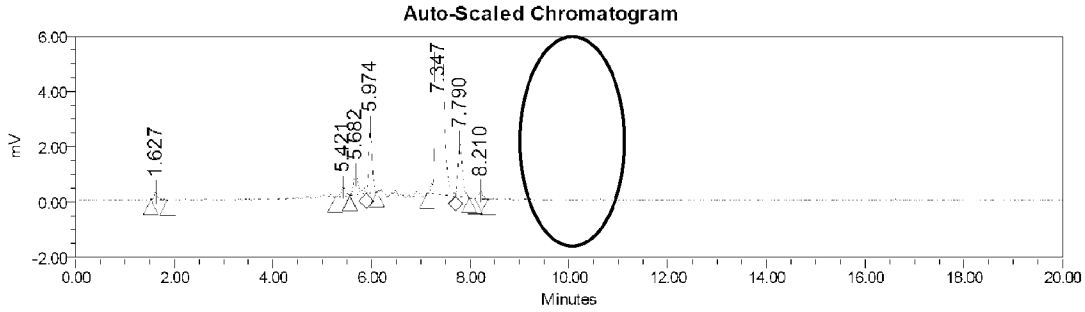
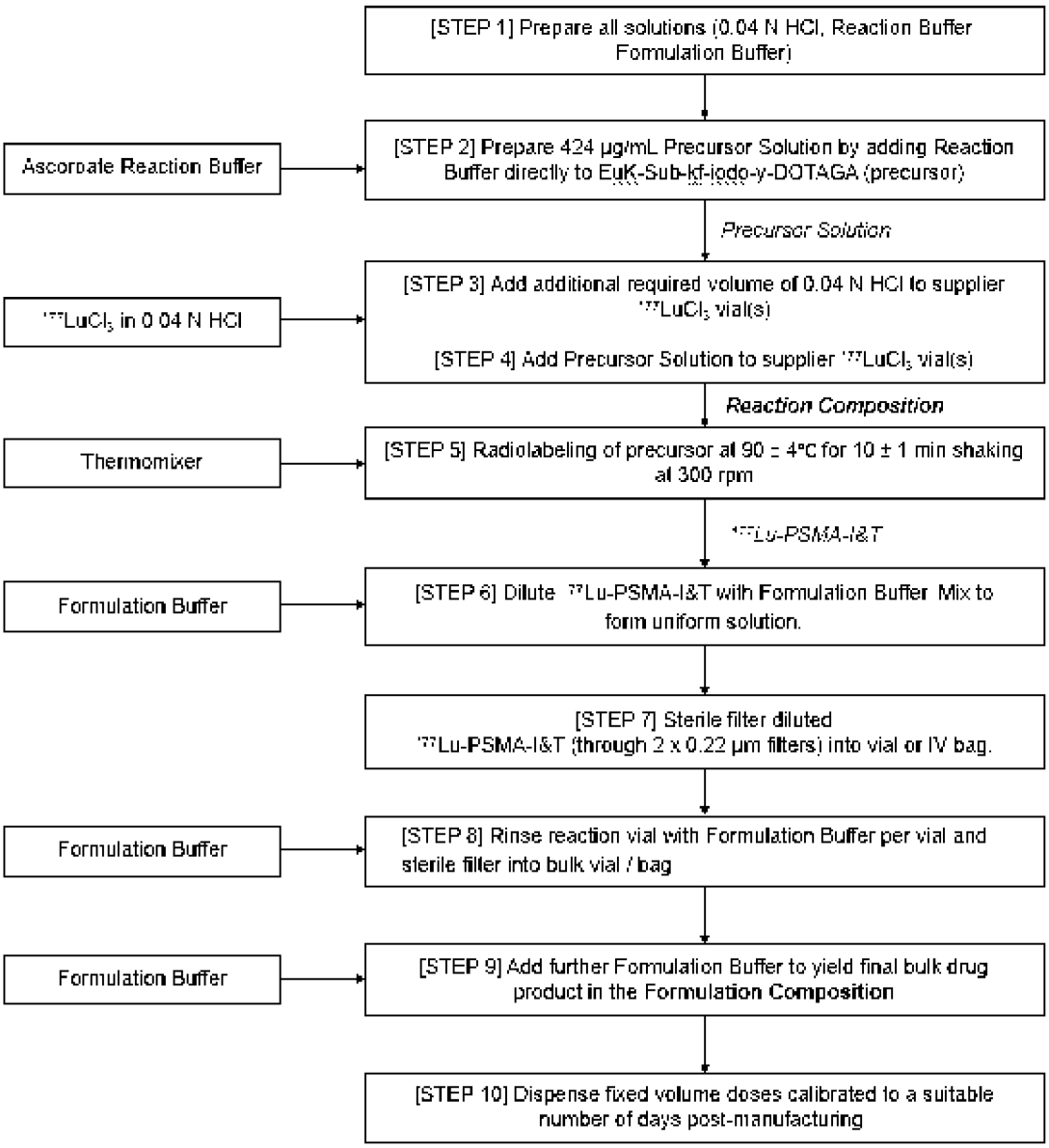


FIG. 2


[STEP 1] Prepare all solutions (0.04 N HCl, Reaction Buffer Formulation Buffer)
Ascorbate Reaction Buffer
[STEP 2] Prepare 424 µg/mL Precursor Solution by adding Reaction Buffer directly to EuK-Sub-kf-iodo-y-DOTAGA (precursor)
Precursor Solution
$^{177}LuCl_3$ in 0.04 N HCl
[STEP 3] Add additional required volume of 0.04 N HCl to supplier $^{177}LuCl_3$ vial(s)
[STEP 4] Add Precursor Solution to supplier $^{177}LuCl_3$ vial(s)
Reaction Composition
Thermomixer
[STEP 5] Radiolabeling of precursor at 90 ± 4°C for 10 ± 1 min shaking at 300 rpm
^{177}Lu-PSMA-I&T
Formulation Buffer
[STEP 6] Dilute ^{177}Lu-PSMA-I&T with Formulation Buffer. Mix to form uniform solution.
[STEP 7] Sterile filter diluted ^{177}Lu-PSMA-I&T (through 2 x 0.22 µm filters) into vial or IV bag.
Formulation Buffer
[STEP 8] Rinse reaction vial with Formulation Buffer per vial and sterile filter into bulk vial / bag
Formulation Buffer
[STEP 9] Add further Formulation Buffer to yield final bulk drug product in the Formulation Composition
[STEP 10] Dispense fixed volume doses calibrated to a suitable number of days post-manufacturing