

PSMA-TARGETED RADIOPHARMACEUTICALS FOR TREATMENT OF CANCER**CROSS-REFERENCE TO RELATED APPLICATIONS**

5 This application claims the benefit of U.S. Provisional Patent Application No. 63/515,943, filed on July 27, 2023, the entire content of which is incorporated by reference herein.

BACKGROUND

As a transmembrane glycoprotein, prostate-specific membrane antigen (PSMA) is significantly overexpressed in high grade and advanced stage prostate cancer, thereby making it
10 an attractive target for diagnostic and therapeutic approaches.

PSMA has also become one of the most promising molecular targets in nuclear medicine. Various PSMA-targeted radiopharmaceuticals, e.g., radioligand imaging and radioligand therapy, have been developed and transferred to clinical applications. Among them, ¹⁷⁷Lu-PSMA-617 has been recently approved by the FDA to treat progressive, PSMA positive
15 metastatic castration-resistant prostate cancer (mCRPC). ²²⁵Ac-labeled PSMA ligands are widely considered to exert better efficacy in treating prostate cancers due to alpha emission's higher energy, shorter range, and stronger killing effect on tumor cells, as compared to beta emitters such as ¹⁷⁷Lu.

There is a need for improved treatment of PSMA-expressing cancers that exerts superior
20 therapeutic efficacy with acceptable toxicity profiles.

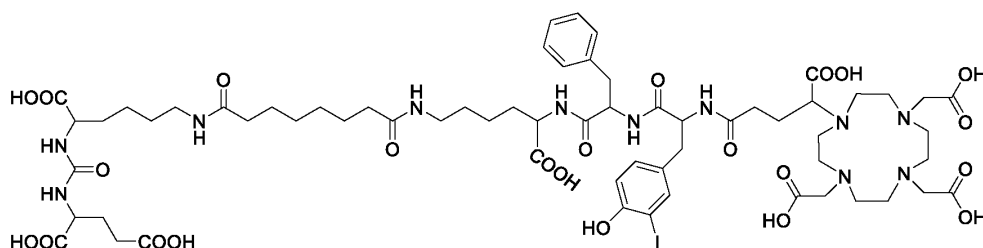
SUMMARY

The present disclosure encompasses the insight that certain pharmaceutical compositions comprising an ²²⁵Ac-PSMA radioligand, i.e., ²²⁵Ac-PSMA-I&T, may provide improved efficacy
25 over beta emitters. Radioactive decay can cause direct physical damage (such as single or double-stranded DNA breaks) or indirect damage (such as by-stander or crossfire effects) to the biomolecules that constitute a cell. Drugs that deliver radionuclides to cancer cells, i.e., radiopharmaceuticals or radioconjugates, provide a mechanism to generate DNA damage with anti-cancer therapeutic effect. The present disclosure provides pharmaceutical compositions

comprising ^{225}Ac -radioconjugate, targeting PSMA positive tumors and using actinium-225 to target cancer cells, to treat or ameliorate cancer, e.g., prostate cancer.

More specifically, provided are pharmaceutical compositions for treating a patient having cancer expressing PSMA, wherein the pharmaceutical composition comprises:

- 5 (a) an ^{225}Ac -radioconjugate or a pharmaceutically acceptable salt thereof, wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with a compound of Formula I, or a prodrug thereof:



(I),

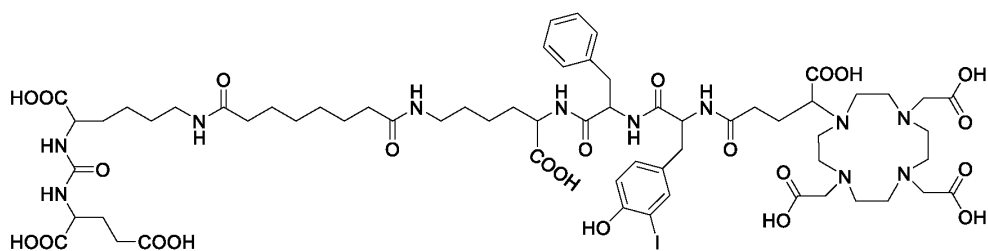
- 10 wherein the ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof is present in the pharmaceutical composition at a concentration of about 1 $\mu\text{g/mL}$ to about 100 $\mu\text{g/mL}$, or in an amount that provides a radioactivity concentration of about 10 $\mu\text{Ci/mL}$ to about 1000 $\mu\text{Ci/mL}$ of the pharmaceutical composition;

- (b) sodium acetate, wherein the sodium acetate is present in the pharmaceutical composition at a concentration of about 1 mg/mL to about 400 mg/mL ,
- 15 (c) sodium L-ascorbate, wherein the sodium L-ascorbate is present in the pharmaceutical composition at a concentration of about 40 mg/mL to about 150 mg/mL ; and
- (d) diethylenetriamine pentaacetate (DTPA), wherein the DTPA is present in the pharmaceutical composition at a concentration of about 5 $\mu\text{g/mL}$ to about 60 $\mu\text{g/mL}$,

- 20 wherein the pharmaceutical composition is an aqueous formulation and is free of a gentisate compound.

In certain embodiments, the pharmaceutical composition comprises:

- (a) an ^{225}Ac -radioconjugate or a pharmaceutically acceptable salt thereof, wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with a compound of Formula
- 25 I, or a prodrug thereof:



(I),

wherein the ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof is present in the pharmaceutical composition at a concentration of about 1 $\mu\text{g/mL}$ to about 100 $\mu\text{g/mL}$, or in an amount that provides a radioactivity concentration of about 10 $\mu\text{Ci/mL}$ to about 1000 $\mu\text{Ci/mL}$ of the pharmaceutical composition;

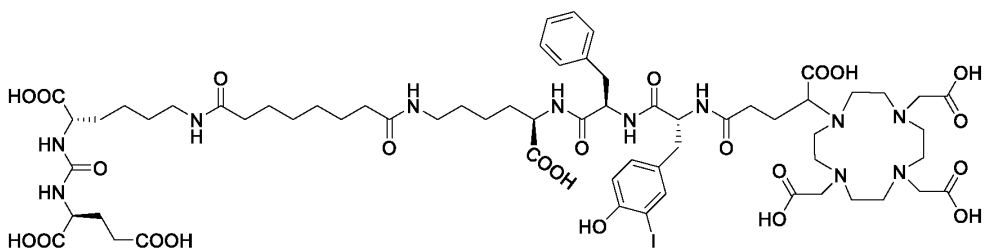
(b) sodium acetate, wherein the sodium acetate is present in the pharmaceutical composition at a concentration of about 1 mg/mL to about 400 mg/mL ,

(c) sodium L-ascorbate, wherein the sodium L-ascorbate is present in the pharmaceutical composition at a concentration of about 40 mg/mL to about 150 mg/mL ; and

(d) diethylenetriamine pentaacetate (DTPA), wherein the DTPA is present in the pharmaceutical composition at a concentration of about 5 $\mu\text{g/mL}$ to about 60 $\mu\text{g/mL}$,

wherein the pharmaceutical composition is an aqueous formulation and is substantially free of a gentisate compound.

In some embodiments, said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure:



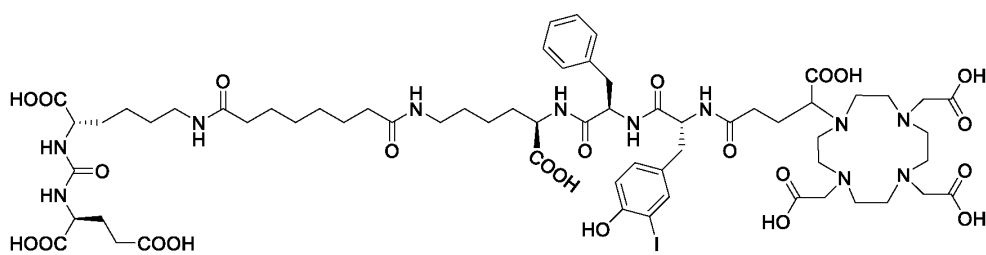
In some embodiments, the pharmaceutical composition further comprises ethanol. In certain embodiments, the ethanol is present in the pharmaceutical composition at a concentration of about 20 mg/mL to about 100 mg/mL . In certain embodiments, the ethanol is present in the pharmaceutical composition at a concentration of about 20 $\mu\text{g/mL}$ to about 20 mg/mL . In certain

embodiments, the ethanol is present in the pharmaceutical composition at a concentration of about 1 µg/mL to about 20 µg/mL.

In some embodiments, the pharmaceutical composition is free of ethanol.

In some embodiments, the pharmaceutical composition comprises:

- 5 (a) ^{225}Ac -radioconjugate or a pharmaceutically acceptable salt thereof, wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure:



wherein the ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof is present in the pharmaceutical composition at a concentration of 7-9 µg/mL;

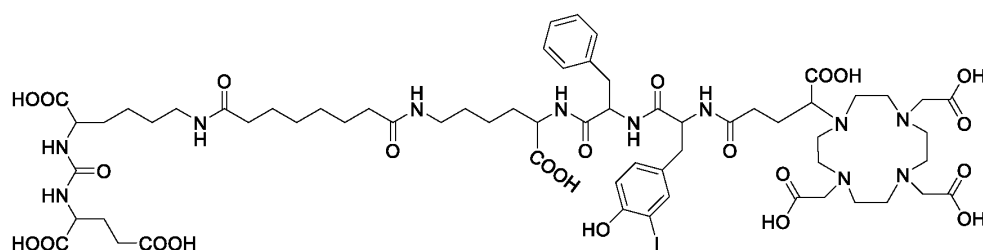
- 10 (b) sodium acetate present in the pharmaceutical composition at a concentration of 7-8 mg/mL,
- (c) sodium L-ascorbate present in the pharmaceutical composition at a concentration of 51-54 mg/mL; and
- (d) diethylenetriamine pentaacetate (DTPA), wherein the DTPA is
- 15 diethylenetriaminepentaacetic acid pentasodium salt, present in the pharmaceutical composition at a concentration of 51-54 µg/mL.

In some embodiments, the pharmaceutical composition retains at least 90% (e.g., at least 92%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) of intact said ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof after 72 hours at about 2 °C to about 25 °C (room temperature) as determined by radio thin-layer chromatography (radio-TLC). In certain embodiments, the pharmaceutical composition retains at least 95% of intact said ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof after 72 hours at about 2 °C to about 25 °C (room temperature) as determined by radio thin-layer chromatography (radio-TLC).

25 In some embodiments, the pharmaceutical composition retains at least 90% (e.g., at least 92%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) of intact said ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof after 7-10 days at

about 2 °C to about 25 °C (room temperature) as determined by radio-TLC. In certain embodiments, the pharmaceutical composition retains at least 95% of intact said ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof after 7-10 days at about 2 °C to about 25 °C (room temperature) as determined by radio thin-layer chromatography (radio-TLC).

- Also covered by this disclosure is a pharmaceutical composition consisting essentially of:
- ^{225}Ac -radioconjugate or a pharmaceutically acceptable salt thereof,
- wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with a compound of Formula I, or a prodrug thereof:



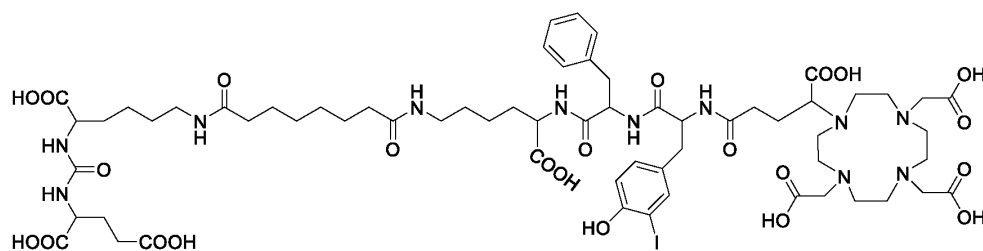
(I),

wherein the ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof is present in the pharmaceutical composition at a concentration of about 1 $\mu\text{g/mL}$ to about 100 $\mu\text{g/mL}$, or in an amount that provides a radioactivity concentration of about 10 $\mu\text{Ci/mL}$ to about 1000 $\mu\text{Ci/mL}$ of the pharmaceutical composition;

- sodium acetate, wherein the sodium acetate is present in the pharmaceutical composition at a concentration of about 1 mg/mL to about 400 mg/mL ,
 - sodium L-ascorbate, wherein the sodium L-ascorbate is present in the pharmaceutical composition at a concentration of about 40 mg/mL to about 150 mg/mL ; and
 - diethylenetriamine pentaacetate (DTPA), wherein the DTPA is present in the pharmaceutical composition at a concentration of about 5 $\mu\text{g/mL}$ to about 60 $\mu\text{g/mL}$,
- wherein the pharmaceutical composition is an aqueous formulation and is free of a gentisate compound.

In certain embodiments, the pharmaceutical composition consists essentially of:

- ^{225}Ac -radioconjugate or a pharmaceutically acceptable salt thereof,
- wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with a compound of Formula I, or a prodrug thereof:



(I),

wherein the ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof is present in the pharmaceutical composition at a concentration of about 1 $\mu\text{g/mL}$ to about 100 $\mu\text{g/mL}$, or in an amount that provides a radioactivity concentration of about 10 $\mu\text{Ci/mL}$ to about 1000 $\mu\text{Ci/mL}$ of the pharmaceutical composition;

(b) sodium acetate, wherein the sodium acetate is present in the pharmaceutical composition at a concentration of about 1 mg/mL to about 400 mg/mL ,

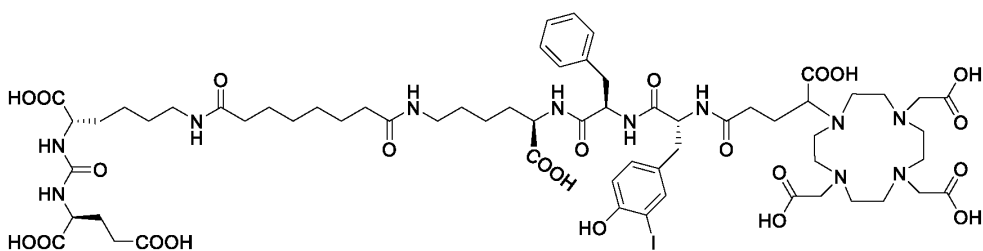
(c) sodium L-ascorbate, wherein the sodium L-ascorbate is present in the pharmaceutical composition at a concentration of about 40 mg/mL to about 150 mg/mL ; and

(d) diethylenetriamine pentaacetate (DTPA), wherein the DTPA is present in the pharmaceutical composition at a concentration of about 5 $\mu\text{g/mL}$ to about 60 $\mu\text{g/mL}$,

wherein the pharmaceutical composition is an aqueous formulation and is substantially free of a gentisate compound.

In certain embodiments, the pharmaceutical composition consisting essentially of the above components features that:

(a) said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure:



wherein the ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof is present in the pharmaceutical composition at a concentration of 7-9 $\mu\text{g/mL}$;

(b) said sodium acetate is present in the pharmaceutical composition at a concentration of 7-8 mg/mL ,

(c) said sodium L-ascorbate is present in the pharmaceutical composition at a concentration of 51-54 mg/mL; and

(d) said DTPA is diethylenetriaminepentaacetic acid pentasodium salt, present in the pharmaceutical composition at a concentration of 51-54 µg/mL.

5 Still within the scope of this disclosure is a method for treating a patient having cancer expressing Prostate Specific Membrane Antigen (PSMA), wherein the method comprises administering to the patient in need thereof a therapeutically effective amount of one of the pharmaceutical compositions provided herein.

10 In some embodiments, the PSMA expressing cancer is selected from the group consisting of prostate cancer, breast cancer, colorectal cancer, renal cell cancer, bladder cancer, testicular cancer, neuroendocrine cancer, and brain tumor. In certain embodiments, the PSMA expressing cancer is prostate cancer, e.g., metastatic castration-resistant prostate cancer (mCRPC).

The present disclosure also covers a method for preparing an ^{225}Ac -PSMA I&T composition, comprising:

15 (a) radiolabeling PSMA I&T with ^{225}Ac in a reaction buffer solution in the absence of a gentisate compound, wherein the reaction buffer solution comprises sodium acetate and sodium L-ascorbate;

(b) heating the mixture from step (a) for a pre-determined time to form a radiolabeled product; and

20 (c) mixing the radiolabeled product with a formulation buffer solution to form an ^{225}Ac -PSMA I&T composition, wherein the formulation buffer solution comprises sodium L-ascorbate and diethylenetriaminepentaacetic acid pentasodium salt.

DETAILED DESCRIPTION

25 The present disclosure relates to certain pharmaceutical compositions comprising an ^{225}Ac -radioconjugate of Formula I, e.g., ^{225}Ac -PSMA-I&T, that can be used for treating PSMA expressing cancer with improved therapeutic efficacy, as compared to existing therapies.

Definitions

Chemical Terms

The term “isomer,” as used herein, means any tautomer, stereoisomer, enantiomer, or diastereomer of any compound. It is recognized that the compound of Formula I has one or more chiral centers and, therefore, can exist as stereoisomers, such as diastereomers (e.g., enantiomers (i.e., (+) or (-))). Unless otherwise noted, chemical structures depicted herein encompass all of the corresponding stereoisomers, that is, both the stereomerically pure form (e.g., geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric and stereoisomeric mixtures, e.g., racemates. Enantiomeric and stereoisomeric mixtures of compounds can typically be resolved into their component enantiomers or stereoisomers by well-known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and stereoisomers can also be obtained from stereomerically or enantiomerically pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

The term “stereoisomer,” as used herein, refers to all possible different isomeric as well as conformational forms which a compound may possess (e.g., a compound of any formula described herein), in particular all possible stereochemically and conformationally isomeric forms, all diastereomers, enantiomers and/or conformers of the basic molecular structure. Some compounds may exist in different tautomeric forms, all of the latter being included within the scope of the present disclosure.

The term “diastereomer,” as used herein means stereoisomers that are not mirror images of one another and are non-superimposable on one another.

The term “enantiomer,” as used herein, means each individual optically active form of a compound, having an optical purity or enantiomeric excess (as determined by methods standard in the art) of at least 80% (i.e., at least 90% of one enantiomer and at most 10% of the other enantiomer), preferably at least 90% and more preferably at least 98%.

Other terms

As used herein, the term “about” or “approximately” refers to a $\pm 10\%$ variation from the recited quantitative value (and includes the recited quantitative value itself) unless otherwise indicated or inferred from the context. For example, unless otherwise stated or inferred from the

context, a concentration of about 100 µg/mL indicates a concentration range of 100±10% µg/mL, i.e., from 90 µg/mL to 110 µg/mL, inclusive.

As used herein, “administering” an agent to a subject includes contacting cells of said subject with the agent.

5 The term “cancer” refers to any cancer caused by the proliferation of malignant neoplastic cells, such as tumors, neoplasms, carcinomas, sarcomas, leukemias, and lymphomas. A “solid tumor cancer” is a cancer comprising an abnormal mass of tissue, e.g., sarcomas, carcinomas, and lymphomas. A “hematological cancer” or “liquid cancer,” as used interchangeably herein, is a cancer present in a body fluid, e.g., lymphomas and leukemias.

10 The term “chelate” as used herein, refers to an organic compound or portion thereof that can be bonded to a central metal or radiometal atom at two or more points.

The term “conjugate,” as used herein, refers to a molecule that contains a chelating group or metal complex thereof, a linker group, and which optionally contains a therapeutic moiety or a targeting moiety.

15 As used herein, the term “compound,” is meant to include all stereoisomers, geometric isomers, and tautomers of the structures depicted.

The compounds described herein can be asymmetric (*e.g.*, having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present disclosure that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present disclosure. Cis and trans geometric isomers of the compounds of the present disclosure are described and may be isolated as a mixture of isomers or as separated isomeric forms.

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Compounds of the present disclosure also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond and the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Examples prototropic tautomers include ketone – enol pairs, amide – imidic acid pairs, lactam – lactim pairs, amide –

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imidic acid pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, such as, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

5 As used herein, the terms “decrease,” “decreased,” “increase,” “increased,” or “reduction,” “reduced,” (e.g., in reference to therapeutic outcomes or effects) have meanings relative to a reference level. In some embodiments, the reference level is a level as determined by the use of said method with a control in an experimental animal model or clinical trial. In some embodiments, the reference level is a level in the same subject before or at the beginning of
10 treatment. In some embodiments, the reference level is the average level in a population not being treated by said method of treatment.

 The term an “effective amount” of an agent (e.g., any of the foregoing conjugates), as used herein, is that amount sufficient to effect beneficial or desired results, such as clinical results, and, as such, an “effective amount” depends upon the context in which it is being
15 applied.

 The term “pharmaceutical composition,” as used herein, represents a composition containing a compound described herein formulated with a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is manufactured or sold with the approval of a governmental regulatory agency as part of a therapeutic regimen for the
20 treatment of disease in a mammal. Pharmaceutical compositions can be formulated, for example, for oral administration in unit dosage form (e.g., a tablet, capsule, caplet, gelcap, or syrup); for topical administration (e.g., as a cream, gel, lotion, or ointment); for intravenous administration (e.g., as a sterile solution free of particulate emboli and in a solvent system suitable for intravenous use); or in any other formulation described herein.

25 A “pharmaceutically acceptable excipient,” as used herein, refers any ingredient other than the compounds described herein (for example, a vehicle capable of suspending or dissolving the active compound) and having the properties of being nontoxic and non-inflammatory in a patient. A pharmaceutically acceptable excipient is typically added to a drug product to help facilitate the formulation, stability, or delivery of the drug. Excipients may include, for example:
30 antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluent), film formers or coatings, flavors, fragrances, glidants

(flow enhancers), lubricants, preservatives, printing inks, radioprotectants, sorbents, suspending or dispersing agents, sweeteners, or waters of hydration. Exemplary excipients include, but are not limited to: ascorbic acid, histidine, phosphate buffer, butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

The term “pharmaceutically acceptable salt,” as use herein, represents those salts of the compounds described here that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, or allergic response. Pharmaceutically acceptable salts are well known in the art. For example, pharmaceutically acceptable salts are described in: Berge et al., *J. Pharmaceutical Sciences* 66:1-19, 1977 and in *Pharmaceutical Salts: Properties, Selection, and Use*, (Eds. P.H. Stahl and C.G. Wermuth), Wiley-VCH, 2008. The salts can be prepared in situ during the final isolation and purification of the compounds described herein or separately by reacting the free base group with a suitable organic acid.

Compounds may have ionizable groups so as to be capable of preparation as pharmaceutically acceptable salts. These salts may be acid addition salts involving inorganic or organic acids or the salts may, in the case of acidic forms of compounds, be prepared from inorganic or organic bases. Frequently, the compounds are prepared or used as pharmaceutically acceptable salts prepared as addition products of pharmaceutically acceptable acids or bases. Suitable pharmaceutically acceptable acids and bases are well-known in the art, such as hydrochloric, sulphuric, hydrobromic, acetic, lactic, citric, or tartaric acids for forming acid addition salts, and potassium hydroxide, sodium hydroxide, ammonium hydroxide, caffeine, various amines for forming basic salts. Methods for preparation of the appropriate salts are well-established in art.

Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, among others. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, and magnesium, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, and ethylamine.

The term “radiopharmaceutical” or “radioconjugate,” as used herein, refers to any compound or conjugate that includes a radioisotope or radionuclide, such as the radioisotope or radionuclide described herein.

The term “prodrug,” as used herein, refers to a pharmacologically inactive compound or medication that is administered in its inactive form, and it is converted into a pharmacologically active drug inside the body through metabolism or other chemical reactions.

The term “aqueous formulation,” as used herein, refers to a liquid or semi-solid dosage form that contains water as the primary solvent or medium. Examples of aqueous formulations include solutions, suspensions, emulsions, and gels. In a solution, the drug or active ingredient is dissolved in water; while in a suspension, the drug is suspended in water with the aid of a stabilizer. In an emulsion, the drug is dispersed in water using a surfactant and an emulsifying agent. Gels are semi-solid aqueous formulations that contain a gelling agent to provide a thickened consistency.

The term “substantially free,” as used herein, when used in relation to a given component of a composition (e.g. a pharmaceutical composition substantially free of a gentisate compound), refers to a composition to which essentially none of said component has been added. When a composition is “substantially free” of a given component, said composition suitably comprises no more than 0.001 wt % of said component, suitably no more than 0.0001 wt % of said

component, suitably no more than 0.00001 wt %, suitably no more than 0.000001 wt %, suitably no more than 0.0000001 wt % thereof, most suitably no more than 0.0001 parts per billion (by weight).

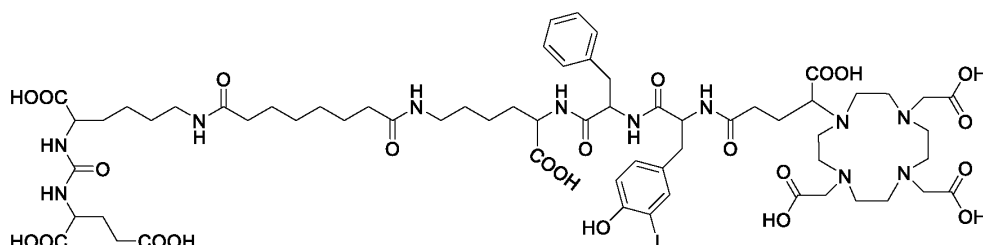
As used herein, and as well understood in the art, “to treat” a condition or “treatment” of the condition (e.g., the conditions described herein such as cancer) is an approach for obtaining beneficial or desired results, such as clinical results. Beneficial or desired results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions; diminishment of extent of disease, disorder, or condition; stabilized (i.e., not worsening) state of disease, disorder, or condition; preventing spread of disease, disorder, or condition; delay or slowing the progress of the disease, disorder, or condition; amelioration or palliation of the disease, disorder, or condition; and remission (whether partial or total), whether detectable or undetectable. In the context of cancer treatment, “ameliorating” may include, for example, reducing incidence of metastases, reducing tumor volume, reducing tumor vascularization and/or reducing the rate of tumor growth. “Palliating” a disease, disorder, or condition means that the extent and/or undesirable clinical manifestations of the disease, disorder, or condition are lessened and/or time course of the progression is slowed or lengthened, as compared to the extent or time course in the absence of treatment.

Pharmaceutical Compositions

The present disclosure provides pharmaceutical compositions comprising an ^{225}Ac -radioconjugate of Formula I in the absence of a gentisate compound. The pharmaceutical compositions can be used for treating a patient having cancer expressing PSMA.

The pharmaceutical composition as disclosed herein comprises:

- (a) an ^{225}Ac -radioconjugate or a pharmaceutically acceptable salt thereof,
 wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with a compound of Formula I, or a prodrug thereof:



(I),

wherein the ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof is present in the pharmaceutical composition at a concentration of about 1 $\mu\text{g/mL}$ to about 100 $\mu\text{g/mL}$, or in an amount that provides a radioactivity concentration of about 10 $\mu\text{Ci/mL}$ to about 1000 $\mu\text{Ci/mL}$ of the pharmaceutical composition;

(b) sodium acetate, wherein the sodium acetate is present in the pharmaceutical composition at a concentration of about 1 mg/mL to about 400 mg/mL ,

(c) sodium L-ascorbate, wherein the sodium L-ascorbate is present in the pharmaceutical composition at a concentration of about 40 mg/mL to about 150 mg/mL ; and

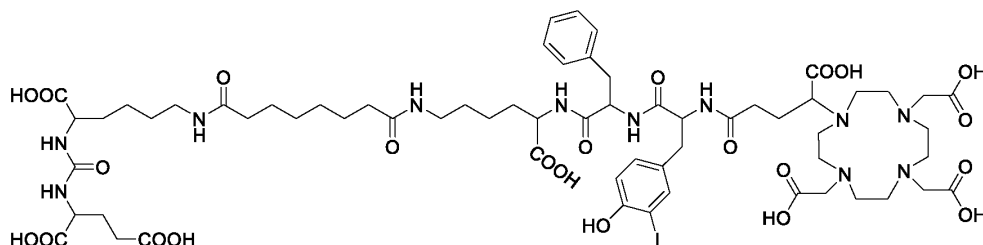
(d) diethylenetriamine pentaacetate (DTPA), wherein the DTPA is present in the pharmaceutical composition at a concentration of about 5 $\mu\text{g/mL}$ to about 60 $\mu\text{g/mL}$,

wherein the pharmaceutical composition is an aqueous formulation and is free of a gentisate compound.

In certain embodiments, the pharmaceutical composition as disclosed herein comprises:

(b) an ^{225}Ac -radioconjugate or a pharmaceutically acceptable salt thereof,

wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with a compound of Formula I, or a prodrug thereof:



(I),

wherein the ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof is present in the pharmaceutical composition at a concentration of about 1 $\mu\text{g/mL}$ to about 100 $\mu\text{g/mL}$, or in an amount that provides a radioactivity concentration of about 10 $\mu\text{Ci/mL}$ to about 1000 $\mu\text{Ci/mL}$ of the pharmaceutical composition;

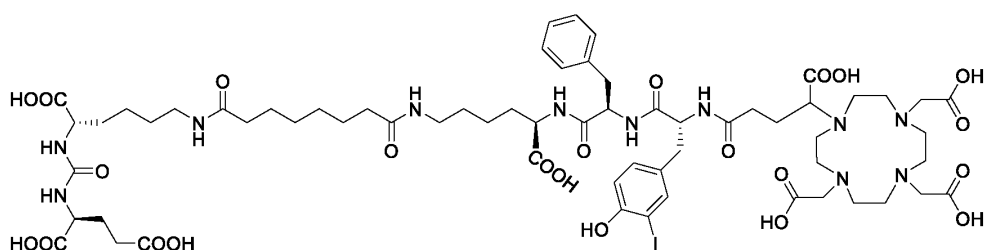
(b) sodium acetate, wherein the sodium acetate is present in the pharmaceutical composition at a concentration of about 1 mg/mL to about 400 mg/mL ,

(c) sodium L-ascorbate, wherein the sodium L-ascorbate is present in the pharmaceutical composition at a concentration of about 40 mg/mL to about 150 mg/mL ; and

(d) diethylenetriamine pentaacetate (DTPA), wherein the DTPA is present in the pharmaceutical composition at a concentration of about 5 $\mu\text{g/mL}$ to about 60 $\mu\text{g/mL}$, wherein the pharmaceutical composition is an aqueous formulation and is substantially free of a gentisate compound.

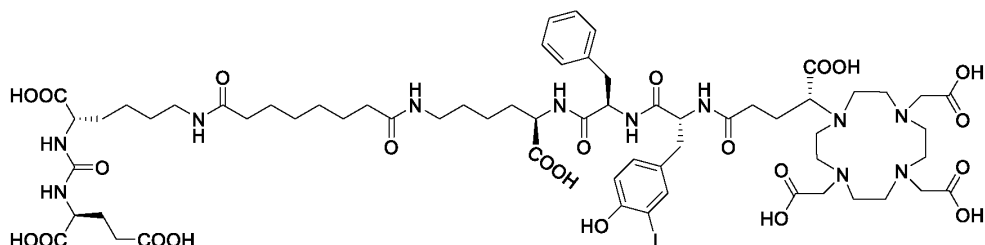
5 Compounds of Formula I include various stereoisomers, e.g., diastereomers or enantiomers, of the structure of Formula I.

In some embodiments, said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure, i.e., PSMA I&T:



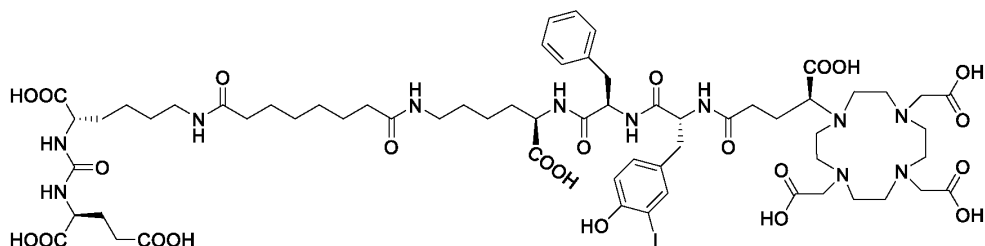
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In certain embodiments, said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure, i.e., PSMA I&T in (*R*)-enantiomeric form with respect to the stereocenter on the carbon adjacent to the DOTA:



15

In certain embodiments, said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure, i.e., PSMA I&T in (*S*)-enantiomeric form with respect to the stereocenter on the carbon adjacent to the DOTA:



In some embodiments, the ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof is present in the pharmaceutical composition at a concentration of about 1 $\mu\text{g/mL}$ to about 100 $\mu\text{g/mL}$, e.g., about 2 $\mu\text{g/mL}$ to about 90 $\mu\text{g/mL}$, about 3 $\mu\text{g/mL}$ to about 80 $\mu\text{g/mL}$,
5 about 4 $\mu\text{g/mL}$ to about 60 $\mu\text{g/mL}$, about 5 $\mu\text{g/mL}$ to about 50 $\mu\text{g/mL}$, about 6 $\mu\text{g/mL}$ to about 40 $\mu\text{g/mL}$, about 7 $\mu\text{g/mL}$ to about 30 $\mu\text{g/mL}$, about 8 $\mu\text{g/mL}$ to about 20 $\mu\text{g/mL}$, about 8 $\mu\text{g/mL}$ to about 10 $\mu\text{g/mL}$, about 7 $\mu\text{g/mL}$ to about 10 $\mu\text{g/mL}$, about 6 $\mu\text{g/mL}$ to about 10 $\mu\text{g/mL}$, about 5 $\mu\text{g/mL}$ to about 10 $\mu\text{g/mL}$, about 4 $\mu\text{g/mL}$ to about 10 $\mu\text{g/mL}$, about 3 $\mu\text{g/mL}$ to about 10 $\mu\text{g/mL}$, about 2 $\mu\text{g/mL}$ to about 10 $\mu\text{g/mL}$, about 1 $\mu\text{g/mL}$ to about 10 $\mu\text{g/mL}$, about 10 $\mu\text{g/mL}$
10 to about 15 $\mu\text{g/mL}$, about 15 $\mu\text{g/mL}$ to about 20 $\mu\text{g/mL}$, about 20 $\mu\text{g/mL}$ to about 25 $\mu\text{g/mL}$, about 25 $\mu\text{g/mL}$ to about 30 $\mu\text{g/mL}$, about 30 $\mu\text{g/mL}$ to about 35 $\mu\text{g/mL}$, about 35 $\mu\text{g/mL}$ to about 40 $\mu\text{g/mL}$, about 40 $\mu\text{g/mL}$ to about 45 $\mu\text{g/mL}$, about 45 $\mu\text{g/mL}$ to about 50 $\mu\text{g/mL}$, about 50 $\mu\text{g/mL}$ to about 55 $\mu\text{g/mL}$, about 55 $\mu\text{g/mL}$ to about 60 $\mu\text{g/mL}$, about 60 $\mu\text{g/mL}$ to about 65 $\mu\text{g/mL}$, about 65 $\mu\text{g/mL}$ to about 70 $\mu\text{g/mL}$, about 70 $\mu\text{g/mL}$ to about 75 $\mu\text{g/mL}$, about 75
15 $\mu\text{g/mL}$ to about 80 $\mu\text{g/mL}$, about 80 $\mu\text{g/mL}$ to about 85 $\mu\text{g/mL}$, about 85 $\mu\text{g/mL}$ to about 90 $\mu\text{g/mL}$, about 90 $\mu\text{g/mL}$ to about 95 $\mu\text{g/mL}$, about 95 $\mu\text{g/mL}$ to about 100 $\mu\text{g/mL}$, about 10 $\mu\text{g/mL}$ to about 20 $\mu\text{g/mL}$, about 20 $\mu\text{g/mL}$ to about 30 $\mu\text{g/mL}$, about 30 $\mu\text{g/mL}$ to about 40 $\mu\text{g/mL}$, about 40 $\mu\text{g/mL}$ to about 50 $\mu\text{g/mL}$, about 50 $\mu\text{g/mL}$ to about 60 $\mu\text{g/mL}$, about 60 $\mu\text{g/mL}$ to about 70 $\mu\text{g/mL}$, about 70 $\mu\text{g/mL}$ to about 80 $\mu\text{g/mL}$, about 80 $\mu\text{g/mL}$ to about 90
20 $\mu\text{g/mL}$, or about 90 $\mu\text{g/mL}$ to about 100 $\mu\text{g/mL}$.

In certain embodiments, the ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof is present in the pharmaceutical composition at a concentration of about 5 $\mu\text{g/mL}$ to about 50 $\mu\text{g/mL}$ (e.g., about 5 $\mu\text{g/mL}$ to about 45 $\mu\text{g/mL}$, about 5 $\mu\text{g/mL}$ to about 40 $\mu\text{g/mL}$, about 5 $\mu\text{g/mL}$ to about 35 $\mu\text{g/mL}$, about 5 $\mu\text{g/mL}$ to about 30 $\mu\text{g/mL}$, about 5 $\mu\text{g/mL}$ to about
25 25 $\mu\text{g/mL}$, about 5 $\mu\text{g/mL}$ to about 20 $\mu\text{g/mL}$).

In certain embodiments, the ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof is present in the pharmaceutical composition at a concentration of about 5 $\mu\text{g/mL}$ to about 20 $\mu\text{g/mL}$ (e.g., about 5 $\mu\text{g/mL}$ to about 10 $\mu\text{g/mL}$).

In certain embodiments, the ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt
30 thereof is present in the pharmaceutical composition at a concentration of about 7 $\mu\text{g/mL}$ to about 9 $\mu\text{g/mL}$. In certain embodiments, the ^{225}Ac -radioconjugate or the pharmaceutically

acceptable salt thereof is present in the pharmaceutical composition at a concentration of about 7 $\mu\text{g/mL}$ to about 8 $\mu\text{g/mL}$ (e.g., 7.0 $\mu\text{g/mL}$, 7.1 $\mu\text{g/mL}$, 7.2 $\mu\text{g/mL}$, 7.3 $\mu\text{g/mL}$, 7.4 $\mu\text{g/mL}$, 7.5 $\mu\text{g/mL}$, 7.6 $\mu\text{g/mL}$, 7.7 $\mu\text{g/mL}$, 7.8 $\mu\text{g/mL}$, 7.9 $\mu\text{g/mL}$, or 8.0 $\mu\text{g/mL}$). In certain embodiments, the ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof is present in the

5 pharmaceutical composition at a concentration of about 8 $\mu\text{g/mL}$ to about 9 $\mu\text{g/mL}$ (e.g., 8.1 $\mu\text{g/mL}$, 8.2 $\mu\text{g/mL}$, 8.3 $\mu\text{g/mL}$, 8.4 $\mu\text{g/mL}$, 8.5 $\mu\text{g/mL}$, 8.6 $\mu\text{g/mL}$, 8.7 $\mu\text{g/mL}$, 8.8 $\mu\text{g/mL}$, 8.9 $\mu\text{g/mL}$, or 9.0 $\mu\text{g/mL}$).

In some embodiments, the ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof is in an amount that provides a radioactivity concentration of about 10 $\mu\text{Ci/mL}$ to about
10 1000 $\mu\text{Ci/mL}$, e.g., about 10 $\mu\text{Ci/mL}$ to about 50 $\mu\text{Ci/mL}$, about 50 $\mu\text{Ci/mL}$ to about 100 $\mu\text{Ci/mL}$, about 100 $\mu\text{Ci/mL}$ to about 150 $\mu\text{Ci/mL}$, about 150 $\mu\text{Ci/mL}$ to about 200 $\mu\text{Ci/mL}$, about 200 $\mu\text{Ci/mL}$ to about 250 $\mu\text{Ci/mL}$, about 250 $\mu\text{Ci/mL}$ to about 300 $\mu\text{Ci/mL}$, about 300 $\mu\text{Ci/mL}$ to about 350 $\mu\text{Ci/mL}$, about 350 $\mu\text{Ci/mL}$ to about 400 $\mu\text{Ci/mL}$, about 400 $\mu\text{Ci/mL}$ to about 450 $\mu\text{Ci/mL}$, about 450 $\mu\text{Ci/mL}$ to about 500 $\mu\text{Ci/mL}$, about 500 $\mu\text{Ci/mL}$ to about 550
15 $\mu\text{Ci/mL}$, about 550 $\mu\text{Ci/mL}$ to about 600 $\mu\text{Ci/mL}$, about 600 $\mu\text{Ci/mL}$ to about 650 $\mu\text{Ci/mL}$, about 650 $\mu\text{Ci/mL}$ to about 700 $\mu\text{Ci/mL}$, about 700 $\mu\text{Ci/mL}$ to about 750 $\mu\text{Ci/mL}$, about 750 $\mu\text{Ci/mL}$ to about 800 $\mu\text{Ci/mL}$, about 800 $\mu\text{Ci/mL}$ to about 850 $\mu\text{Ci/mL}$, about 850 $\mu\text{Ci/mL}$ to about 900 $\mu\text{Ci/mL}$, about 900 $\mu\text{Ci/mL}$ to about 950 $\mu\text{Ci/mL}$, or about 950 $\mu\text{Ci/mL}$ to about 1000 $\mu\text{Ci/mL}$.

20 In the pharmaceutical compositions disclosed herein, the sodium acetate is present as a buffer or pH stabilizer. Other equivalent excipients that can be used as a buffer or pH stabilizer include, but are not limited to, acetic acid, sodium ascorbate, ascorbic acid, fumaric acid, propionic acid, ascorbic acid, ammonium sulfate, ammonium hydroxide, arginine, aspartic acid, benzene sulfonic acid, sodium benzoate, sodium bicarbonate, boric acid, sodium carbonate,
25 carbonic acid, diethanolamine, citrate acid, hydrobromic acid, glycine, histidine, sodium lactate, (L)-lysine, maleic acid, methane sulfonic acid, phosphate acid, monobasic sodium phosphate acid, tribasic sodium phosphate acid, dibasic sodium phosphate acid, sodium hydroxide, sodium/disodium succinate, sulfuric acid, sodium tartrate, tartaric acid, and tromethamine (tris).

In some embodiments, the sodium acetate is present in the pharmaceutical composition at
30 a concentration of about 5 mg/mL to about 200 mg/mL , e.g., about 5 mg/mL to about 15 mg/mL , about 15 mg/mL to about 25 mg/mL , about 25 mg/mL to about 35 mg/mL , about 35 mg/mL to

about 45 mg/mL, about 45 mg/mL to about 55 mg/mL, about 55 mg/mL to about 65 mg/mL, about 65 mg/mL to about 75 mg/mL, about 75 mg/mL to about 85 mg/mL, about 85 mg/mL to about 95 mg/mL, about 95 mg/mL to about 100 mg/mL, about 100 mg/mL to about 110 mg/mL, about 110 mg/mL to about 120 mg/mL, about 120 mg/mL to about 130 mg/mL, about 130
5 mg/mL to about 140 mg/mL, about 140 mg/mL to about 150 mg/mL, about 150 mg/mL to about 160 mg/mL, about 160 mg/mL to about 170 mg/mL, about 170 mg/mL to about 180 mg/mL, about 180 mg/mL to about 190 mg/mL, or about 190 mg/mL to about 200 mg/mL.

In certain embodiments, the sodium acetate is present in the pharmaceutical composition at a concentration of about 6 mg/mL to about 10 mg/mL.

10 In certain embodiments, the sodium acetate is present in the pharmaceutical composition at a concentration of about 9 mg/mL.

In the pharmaceutical compositions disclosed herein, the sodium L-ascorbate is present as a buffer or radioprotectant. Other excipients equivalent to sodium L-ascorbate include, but are not limited to, ascorbic acid, sodium acetate, sodium benzoate, sodium bicarbonate, sodium
15 carbonate, tribasic sodium phosphate acid, dibasic sodium phosphate acid, monobasic sodium phosphate acid, sodium tartrate, sodium lactate, sodium succinate, and disodium succinate.

In some embodiments, the sodium L-ascorbate is present in the pharmaceutical composition at a concentration of about 45 mg/mL to about 100 mg/mL, e.g., about 45 mg/mL to about 50 mg/mL, about 50 mg/mL to about 55 mg/mL, about 55 mg/mL to about 60 mg/mL,
20 about 60 mg/mL to about 65 mg/mL, about 65 mg/mL to about 70 mg/mL, about 70 mg/mL to about 75 mg/mL, about 75 mg/mL to about 80 mg/mL, about 80 mg/mL to about 85 mg/mL, about 85 mg/mL to about 90 mg/mL, about 90 mg/mL to about 95 mg/mL, or about 95 mg/mL to about 100 mg/mL.

In certain embodiments, the sodium L-ascorbate is present in the pharmaceutical
25 composition at a concentration of about 45 mg/mL to about 60 mg/mL.

In certain embodiments, the sodium L-ascorbate is present in the pharmaceutical composition at a concentration of about 50 mg/mL.

In the pharmaceutical compositions disclosed herein, the diethylenetriamine pentaacetate (DTPA) is present as a metal chelator. Other metal chelators equivalent to DTPA include, but
30 are not limited to, diethylenetriaminepentaacetic acid, ethylenediaminetetraacetic acid (EDTA)

and 6,6'-((1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))dipicolinic acid (Macropa), or any pharmaceutically acceptable salt thereof.

In some embodiments, the DTPA is diethylenetriaminepentaacetic acid calcium trisodium salt hydrate (DTPA-CTSH) or diethylenetriaminepentaacetic acid pentasodium salt (DTPA-PS).

5 In certain embodiments, the DTPA is DTPA-PS.

In some embodiments, the DTPA (e.g., DTPA-PS) is present in the pharmaceutical composition at a concentration of about 20 µg/mL to about 55 µg/mL, e.g., about 20 µg/mL to about 25 µg/mL, about 25 µg/mL to about 30 µg/mL, about 30 µg/mL to about 35 µg/mL, about 35 µg/mL to about 40 µg/mL, about 40 µg/mL to about 45 µg/mL, about 45 µg/mL to about 50
10 µg/mL, or about 50 µg/mL to about 55 µg/mL.

In certain embodiments, the DTPA (e.g., DTPA-PS) is present in the pharmaceutical composition at a concentration of about 45 µg/mL to about 52 µg/mL.

In certain embodiments, the DTPA (e.g., DTPA-PS) is present in the pharmaceutical composition at a concentration of about 50 µg/mL.

15 The pharmaceutical compositions disclosed herein can comprise ethanol. In some embodiments, the pharmaceutical compositions are free of ethanol.

In some embodiments, the pharmaceutical compositions further comprise ethanol, wherein the ethanol is present in the pharmaceutical composition at a concentration of about 20 mg/mL to about 100 mg/mL, e.g., about 40 mg/mL to about 100 mg/mL, about 60 mg/mL to about 100 mg/mL, about 80 mg/mL to about 100 mg/mL, about 20 mg/mL to about 40 mg/mL,
20 about 40 mg/mL to about 60 mg/mL, about 60 mg/mL to about 80 mg/mL, about 80 mg/mL to about 100 mg/mL, about 20 mg/mL to about 30 mg/mL, about 30 mg/mL to about 40 mg/mL, about 40 mg/mL to about 50 mg/mL, about 50 mg/mL to about 60 mg/mL, about 60 mg/mL to about 70 mg/mL, about 70 mg/mL to about 80 mg/mL, about 80 mg/mL to about 90 mg/mL, or
25 about 90 mg/mL to about 100 mg/mL.

In certain embodiments, the ethanol is optionally present in the pharmaceutical composition at a concentration of about 20 mg/mL, about 30 mg/mL, about 40 mg/mL, about 50 mg/mL, about 60 mg/mL, about 70 mg/mL, about 80 mg/mL, about 90 mg/mL, or about 100 mg/mL.

In certain embodiments, the ethanol is optionally present in the pharmaceutical composition at a concentration of about 40 mg/mL to about 100 mg/mL or about 20 mg/mL to about 40 mg/mL.

5 In certain embodiments, the ethanol is optionally present in the pharmaceutical composition at a concentration of less than 40 mg/mL.

In some embodiments, the ethanol is present in the pharmaceutical composition at a concentration of about 20 µg/mL to about 20 mg/mL, e.g., about 20 µg/mL to about 200 µg/mL, about 200 µg/mL to about 500 µg/mL, about 500 µg/mL to about 1 mg/mL, about 1 mg/mL to about 10 mg/mL, about 10 mg/mL to about 20 mg/mL, about 20 µg/mL, about 100 µg/mL, about 10 200 µg/mL, about 400 µg/mL, about 600 µg/mL, about 800 µg/mL, about 1 mg/mL, about 2 mg/mL, about 3 mg/mL, about 4 mg/mL, about 5 mg/mL, about 6 mg/mL, about 7 mg/mL, about 8 mg/mL, about 9 mg/mL, about 10 mg/mL, about 12 mg/mL, about 14 mg/mL, about 16 mg/mL, about 18 mg/mL, or about 20 mg/mL.

In some embodiments, the ethanol is optionally present in the pharmaceutical composition at a concentration of about 1 µg/mL to about 20 µg/mL, e.g., about 1 µg/mL to about 5 µg/mL, about 5 µg/mL to about 10 µg/mL, about 10 µg/mL to about 15 µg/mL, about 15 µg/mL to about 20 µg/mL, about 5 µg/mL to about 10 µg/mL, about 1 µg/mL, about 2 µg/mL, about 3 µg/mL, about 4 µg/mL, about 5 µg/mL, about 6 µg/mL, about 7 µg/mL, about 8 µg/mL, about 9 µg/mL, about 10 µg/mL, about 11 µg/mL, about 12 µg/mL, about 13 µg/mL, about 14 20 µg/mL, about 15 µg/mL, about 16 µg/mL, about 17 µg/mL, about 18 µg/mL, about 19 µg/mL, or about 20 µg/mL.

In certain embodiments, the ethanol is optionally present in the pharmaceutical composition at a concentration of about 2 µg/mL to about 10 µg/mL.

25 In certain embodiments, the ethanol is optionally present in the pharmaceutical composition at a concentration of about 5 µg/mL.

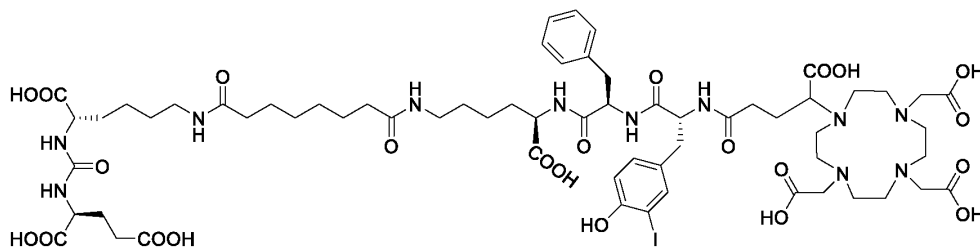
In the pharmaceutical compositions disclosed herein, the aqueous formulation is typically formed in a sodium chloride saline solution, which can be at a concentration of about 0.1% w/w to about 5% w/w (e.g., about 0.1% w/w to about 0.5% w/w, about 0.5% w/w to about 1% w/w, about 1% w/w to about 2% w/w, about 2% w/w to about 3% w/w, about 3% w/w to about 4% 30 w/w, or about 4% w/w to about 5% w/w). In some embodiments, the sodium chloride saline

solution is at a concentration of about 0.5% w/w to about 1% w/w (e.g., about 0.6% w/w, about 0.7% w/w, about 0.8% w/w, about 0.9% w/w).

In some embodiments, the pharmaceutical composition disclosed herein comprises:

(a) ^{225}Ac -radioconjugate or a pharmaceutically acceptable salt thereof,

5 wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure:



wherein the ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof is present in the pharmaceutical composition at a concentration of 7-9 $\mu\text{g/mL}$;

(b) sodium acetate present in the pharmaceutical composition at a concentration of 7-8 mg/mL,

(c) sodium L-ascorbate present in the pharmaceutical composition at a concentration of 51-54 mg/mL; and

(d) diethylenetriamine pentaacetate (DTPA), wherein the DTPA is diethylenetriaminepentaacetic acid pentasodium salt, present in the pharmaceutical composition at a concentration of 51-54 $\mu\text{g/mL}$.

In some embodiments, the pharmaceutical composition has a pH of about 3 to about 9 (e.g., 4 to 9, 5 to 9, 3 to 8, 4 to 8, or 5 to 8). The pH of the pharmaceutical composition may be about 3.5, 4.0, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9 or 9.0, or in a range of any between. In certain embodiments, the pharmaceutical composition has a pH of about 5 to about 8.

In some embodiments, the pharmaceutical composition retains at least 90% (e.g., at least 92%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) of intact said ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof after 72 hours (e.g., after 96 hours, after 120 hours, after 144 hours, after 168 hours, after 192 hours, after 216 hours, or after 240 hours) at about 2 $^{\circ}\text{C}$ to about 25 $^{\circ}\text{C}$ (e.g., about 2 $^{\circ}\text{C}$ to about 5 $^{\circ}\text{C}$, about 2 $^{\circ}\text{C}$

to about 8 °C, about 2 °C to about 10 °C, about 10 °C to about 15 °C, about 15 °C to about 20 °C, or about 20 °C to about 25 °C) as determined by radio thin-layer chromatography (radio-TLC).

5 In certain embodiments, the pharmaceutical composition retains at least 90% (e.g., at least 92%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) of intact said ²²⁵Ac-radioconjugate or the pharmaceutically acceptable salt thereof after 7-10 days (e.g., after 7 days, after 8 days, after 9 days, or after 10 days) at about 2 °C to about 25 °C (e.g., about 2 °C to about 5 °C, about 2 °C to about 8 °C, about 2 °C to about 10 °C, about 10 °C to about 15 °C, about 15 °C to about 20 °C, or about 20 °C to about 25 °C) as determined by radio-TLC.

10 In certain embodiments, the pharmaceutical composition retains at least 90% (e.g., at least 92%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) of intact said ²²⁵Ac-radioconjugate or the pharmaceutically acceptable salt thereof after 7-10 days (e.g., after 7 days, after 8 days, after 9 days, or after 10 days) at about 2 °C to about 8 °C as determined by radio-TLC.

15 In certain embodiments, the pharmaceutical composition retains at least 90% (e.g., at least 92%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) of intact said ²²⁵Ac-radioconjugate or the pharmaceutically acceptable salt thereof after 7-10 days (e.g., after 7 days, after 8 days, after 9 days, or after 10 days) at about 20 °C to about 25 °C as determined by radio-TLC.

20 In certain embodiments, the pharmaceutical composition retains at least 95% of intact said ²²⁵Ac-radioconjugate or the pharmaceutically acceptable salt thereof after 3 days at about 2 °C to about 8 °C as determined by radio-TLC.

In certain embodiments, the pharmaceutical composition retains at least 95% of intact said ²²⁵Ac-radioconjugate or the pharmaceutically acceptable salt thereof after 3 days at about 20
25 °C to about 25 °C as determined by radio-TLC.

In certain embodiments, the pharmaceutical composition retains at least 95% of intact said ²²⁵Ac-radioconjugate or the pharmaceutically acceptable salt thereof after 7-10 days at about 2 °C to about 8 °C as determined by radio-TLC.

30 In certain embodiments, the pharmaceutical composition retains at least 95% of intact said ²²⁵Ac-radioconjugate or the pharmaceutically acceptable salt thereof after 7-10 days at about 20 °C to about 25 °C as determined by radio-TLC.

In certain embodiments, the pharmaceutical composition retains at least 99% of intact said ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof after 3 days (or 72 hours) at about 2 °C to about 8 °C as determined by radio-TLC.

5 In certain embodiments, the pharmaceutical composition retains at least 98% of intact said ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof after 7 days (or 168 hours) at about 2 °C to about 8 °C as determined by radio-TLC.

In certain embodiments, the pharmaceutical composition retains at least 90% of intact said ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof after 10 days (or 240 hours) at about 2 °C to about 8 °C as determined by radio-TLC.

10 In certain embodiments, the pharmaceutical composition retains at least 99% of intact said ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof after 3 days (or 72 hours) at about 20 °C to about 25 °C as determined by radio-TLC.

In certain embodiments, the pharmaceutical composition retains at least 98% of intact said ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof after 7 days (or 168
15 hours) at about 20 °C to about 25 °C as determined by radio-TLC.

In certain embodiments, the pharmaceutical composition retains at least 90% of intact said ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof after 10 days (or 240 hours) at about 20 °C to about 25 °C as determined by radio-TLC.

The present disclosure also covers a method for preparing an ^{225}Ac -PSMA I&T
20 composition set forth above, wherein the method comprises:

(a) radiolabeling PSMA I&T with ^{225}Ac in a reaction buffer solution in the absence of a gentisate compound, wherein the reaction buffer solution comprises sodium acetate and sodium L-ascorbate;

(b) heating the mixture from step (a) for a pre-determined time to form a radiolabeled
25 product; and

(c) mixing the radiolabeled product with a formulation buffer solution to form an ^{225}Ac -PSMA I&T composition, wherein the formulation buffer solution comprises sodium L-ascorbate and diethylenetriaminepentaacetic acid pentasodium salt.

In certain embodiments, the ^{225}Ac used in radiolabeling step (a) is reconstituted in an HCl
30 solution having a concentration of less than 0.05 M (e.g., 0.04 M, 0.03 M, 0.02 M, 0.01 M, 0.005 M, 0.004 M, 0.003 M, 0.002 M, or 0.001 M).

In certain embodiments, the gentisate compound is gentisic acid, thus step (a) is performed in the absence of gentisic acid.

In certain embodiments, the pre-determined time for heating in step (b) is less than 25 minutes (e.g., 20 minutes, 15 minutes, or 10 minutes).

5

Subjects

In the methods disclosed herein, the pharmaceutical composition comprising an ^{225}Ac -radioconjugate of Formula I is administered to a patient having PSMA-expressing cancer or at risk of developing such cancer.

In some embodiments, the patient may have been diagnosed with cancer. The cancer may be a primary cancer or a metastatic cancer. The patient may have any stage of cancer, e.g., stage I, stage II, stage III, or stage IV with or without lymph node involvement and with or without metastases. Provided methods may prevent or reduce further growth of the cancer and/or otherwise ameliorate the cancer (e.g., prevent or reduce metastases). In some

embodiments, the patient does not have cancer but has been determined to be at risk of developing PSMA-expressing cancer, e.g., because of the presence of one or more risk factors such as environmental exposure, presence of one or more genetic mutations or variants, family history, etc.

In some embodiments, the PSMA expressing cancer is selected from the group consisting of prostate cancer, breast cancer, colorectal cancer, renal cell cancer, bladder cancer, testicular cancer, neuroendocrine cancer, and brain tumor.

In some embodiments, the cancer is prostate cancer, e.g., metastatic castration-resistant prostate cancer (mCRPC).

Administration and dosage

Effective or therapeutically effective doses

In some embodiments, therapeutic agents, or pharmaceutical compositions comprising the same, as disclosed herein are administered to a subject in a manner (e.g., dosing amount and timing) sufficient to cure or at least partially arrest the symptoms of the disorder and its complications. In the context of a single therapy (a “monotherapy”), an amount adequate to

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accomplish this purpose is defined as a “therapeutically effective amount,” an amount of a compound sufficient to substantially improve at least one symptom associated with the disease or a medical condition. The “therapeutically effective amount” typically varies depending on the therapeutic. For known therapeutic agents, the relevant therapeutically effective amounts may be
5 known to or readily determined by those of skill in the art.

For example, in the treatment of cancer, an agent or compound that decreases, prevents, delays, suppresses, or arrests any symptom of the disease or condition would be therapeutically effective. A therapeutically effective amount of an agent or compound is not required to cure a disease or condition but will provide a treatment for a disease or condition such that the onset of
10 the disease or condition is delayed, hindered, or prevented, or the disease or condition symptoms are ameliorated, or the term of the disease or condition is changed or, for example, is less severe or recovery is accelerated in an individual. For example, a treatment may be therapeutically effective if it causes a cancer to regress or to slow the cancer’s growth.

The dosage regimen (e.g., amounts of each therapeutic, relative timing of therapies, etc.)
15 that is effective for these uses may depend on the severity of the disease or condition and the weight and general state of the subject. For example, the therapeutically effective amount of a particular composition comprising a therapeutic agent applied to mammals (e.g., humans) can be determined by the person of ordinary skill in the art with consideration of individual differences in age, weight, and the condition of the mammal. Because certain conjugates of the present
20 disclosure exhibit an enhanced ability to target cancer cells and residualize, the dosage of these compounds can be lower than (e.g., less than or equal to about 90%, 75%, 50%, 40%, 30%, 20%, 15%, 12%, 10%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.1% of) the equivalent dose of required for a therapeutic effect of the unconjugated agent. Therapeutically effective and/or optimal amounts can also be determined empirically by those of skill in the art.

25 Single or multiple administrations of a radiopharmaceutical or a composition (e.g., a pharmaceutical composition comprising a therapeutic agent or a radioconjugate disclosed herein) can be carried out with dose levels and pattern being selected by the treating physician. The dose and administration schedule can be determined and adjusted based on the severity of the disease or condition in the subject, which may be monitored throughout the course of treatment
30 according to the methods commonly practiced by clinicians or those described herein.

In some embodiments, the radiopharmaceutical is administered in a single dose. In some embodiments, the radiopharmaceutical is administered more than once, i.e., multiple doses. When the radiopharmaceutical is administered more than once, the dose of each administration may be the same or different.

5 In some embodiments, compositions (such as compositions comprising radioconjugates) are administered for radiation treatment planning or diagnostic purposes. When administered for radiation treatment planning or diagnostic purposes, compositions may be administered to a subject in a diagnostically effective dose and/or an amount effective to determine the therapeutically effective dose. In some embodiments, a first dose of disclosed conjugate or a
10 composition (e.g., pharmaceutical composition) thereof is administered in an amount effective for radiation treatment planning, followed by administration of a second dose of disclosed conjugate or a composition (e.g., pharmaceutical composition) thereof in an amount effective for therapeutic treatment.

Pharmaceutical compositions comprising one or more agents (e.g., ^{225}Ac -radioconjugate)
15 can be formulated for use in accordance with disclosed methods and systems in a variety of drug delivery systems. One or more physiologically acceptable excipients or carriers can also be included in the composition for proper formulation. Examples of suitable formulations are found in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Philadelphia, PA, 17th ed., 1985. For a brief review of methods for drug delivery, see, e.g., Langer (*Science* 249:1527-
20 1533, 1990).

Formulations

Pharmaceutical compositions may be formulated for parenteral, intranasal, topical, oral, or local administration, such as by a transdermal means, for prophylactic and/or therapeutic
25 treatment. Pharmaceutical compositions can be administered parenterally (e.g., by intravenous, intramuscular, or subcutaneous injection), or by oral ingestion, or by topical application or intraarticular injection at areas affected by the vascular or cancer condition. Examples of additional routes of administration include intravascular, intra-arterial, intratumor, intraperitoneal, intraventricular, intraepidural, as well as nasal, ophthalmic, intrascleral,
30 intraorbital, rectal, topical, or aerosol inhalation administration. Also specifically contemplated are sustained release administration, by such means as depot injections or erodible implants or

components. Suitable compositions include compositions comprising include agents (e.g., compounds as disclosed herein) dissolved or suspended in an acceptable carrier, preferably an aqueous carrier, e.g., water, buffered water, saline, or PBS, among others, e.g., for parenteral administration. Compositions may contain pharmaceutically acceptable auxiliary substances to
5 approximate physiological conditions, such as pH adjusting and buffering agents, tonicity adjusting agents, wetting agents, or detergents, among others. In some embodiments, compositions are formulated for oral delivery; for example, compositions may contain inert ingredients such as binders or fillers for the formulation of a unit dosage form, such as a tablet or a capsule. In some embodiments, compositions are formulated for local administration; for
10 example, compositions may contain inert ingredients such as solvents or emulsifiers for the formulation of a cream, an ointment, a gel, a paste, or an eye drop.

Compositions may be sterilized, e.g., by conventional sterilization techniques, or sterile filtered. Aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the
15 preparations typically will be between 3 and 11, more preferably between 5 and 9 or between 6 and 8, and most preferably between 6 and 7, such as 6 to 6.5.

Effects

20 A therapeutic effect refers to the desirable or beneficial effect of a medication or medical treatment in treating a disease, condition, or symptom. It is the intended effect that a medication or treatment is designed to produce in order to improve the health or well-being of a patient.

The therapeutic effect of a medication, or a pharmaceutical composition as disclosed herein, may include relieving symptoms, treating or curing a disease, preventing a condition
25 from getting worse, or improving overall health and quality of life.

The therapeutic effect for cancer patients depends on the type of cancer and the stage of the disease. The goal of cancer treatment is to eliminate or control the cancer cells while minimizing harm to normal, healthy cells in the body. In some embodiments, the therapeutic effect comprises a decrease in tumor volume, a stable tumor volume, or a reduced rate of
30 increase in tumor volume. In some embodiments, the therapeutic effect comprises a decreased incidence of recurrence or metastasis.

Examples

Materials:

The compounds used in the pharmaceutical compositions described herein are made from commercially available chemicals and/or from compounds described in the chemical literature, following standard organic synthesis techniques known to those skilled in this art.

“Commercially available chemicals” can be obtained from standard commercial sources including, but not limited to, ABX advanced biochemical compounds GmbH (Radeberg, Germany), Acros Organics (Pittsburgh, Pa.), Apin Chemicals Ltd. (Milton Park, U.K.), Avidity Science (U.S.A.), Avocado Research (Lancashire, U.K.), BDH, Inc. (Toronto, Canada), Bionet (Cornwall, U.K.), Chem Service Inc. (West Chester, Pa.), Crescent Chemical Co. (Hauppauge, N.Y.), Eastman Organic Chemicals, Eastman Kodak Company (Rochester, N.Y.), Fisher Scientific Co. (Pittsburgh, Pa.), Frontier Scientific (Logan, Utah), ICN Biomedicals, Inc. (Costa Mesa, Calif.), ITM (Munich, Germany), Key Organics (Cornwall, U.K.), Lancaster Synthesis (Windham, N.H.), Parish Chemical Co. (Orem, Utah), Pfaltz & Bauer, Inc. (Waterbury, Conn.), Polyorganix (Houston, Tex.), Pierce Chemical Co. (Rockford, Ill.), Sigma-Aldrich (U.S.A.), Spectrum Quality Product, Inc. (New Brunswick, N.J.), TCI America (Portland, Oreg.), Trans World Chemicals, Inc. (Rockville, Md.), VWR (Radnor, Pa., USA), Wako Chemicals USA, Inc. (Richmond, Va.), and Wuxi-Apptech Inc. (Shanghai, China).

Example 1. Preparation of Pharmaceutical Compositions

Compounds of Formula I are small molecule antagonists targeting PSMA, which can be radiolabeled with a radionuclide such as Actinium-225 (^{225}Ac) to form radionuclide-chelated radiopharmaceuticals. The synthesis of compound of Formula I, or corresponding radionuclide-chelated radiopharmaceuticals, can be referred to the following documents: Weineisen M, et al. *EJNMMI Research*, 2014, 4:63; Weineisen M, et al. *J Nucl Med* 2015, 56:1169–1176; US 11,129,912 B1; and WO 2018/108287 A1.

Pharmaceutical compositions comprising an ^{225}Ac -chelated radioconjugate of Formula I can be prepared by following or referencing to the protocols set forth below.

Preparation of 0.001 M HCl Solution: 4.2 μL of concentrated hydrochloric acid (TraceSelect or equivalent) is added into 37 mL of Water (W8-1), followed by mixing the solution until completely homogeneous. A pH meter is used to confirm that the pH of the buffer solution is 3.0 ± 0.5 .

- 5 **Preparation of 0.05 M HCl Solution:** 220 μL of concentrated hydrochloric acid (TraceSelect or equivalent) is added into 40 mL of Water (W8-1), followed by mixing the solution until completely homogeneous.

- 10 **Preparation of Sodium Acetate – Dissolution Buffer Solution:** 3.9-4.3 g of sodium acetate is transferred to a 150 mL Biotainer. 50 mL of Water (W8-1) is added to the Biotainer using an appropriately sized disposable serological pipette, followed by 68 μL of concentrated hydrochloric acid (TraceSelect or equivalent). The solution is mixed until completely homogeneous. A pH meter is used to confirm that the pH of the buffer solution is 6.5 ± 0.3 .

- 15 **Preparation of Sodium Acetate – Sodium Ascorbate Reaction Buffer Solution:** 0.25-0.27 g of sodium L-ascorbate and 3.9-4.3 g of sodium acetate are transferred to a 50 mL conical tube. 50 mL of Water (W8-1) is added to the Biotainer using an appropriately sized disposable serological pipette, followed by 65 μL of concentrated hydrochloric acid (TraceSelect or equivalent). The solution is mixed until completely homogeneous. A pH meter is used to confirm that the pH of the buffer solution is 6.5 ± 0.3 .

- 20 **Preparation of Ascorbate-DTPA Formulation Buffer Solution:** 17.9–18.1 g of sodium L-ascorbate is transferred to a 500 mL Receiver Bottle. 300 mL of Water (W8-1) is added to the Receiver Bottle using an appropriately sized serological pipette, followed by 45 μL of Pentasodium-DTPA solution (~40% in H_2O) using an appropriately sized calibrated pipette. 7.5 mL of 0.05 M hydrochloric acid is added to the receiver bottle using an appropriately sized disposable serological pipette. The receiver bottle is closed and the resulting solution is swirled until completely homogeneous. A pH meter is used to confirm that the pH of the buffer solution is 6.5 ± 0.3 .

Reconstitution of Ac-225 Vial: A calibrated pipettor is used to transfer 0.001 M HCl solution to a v-vial containing [Ac-225] ([Ac-225] source vial) such that the radioactivity concentration in the [Ac-225] source vial is 2.04 $\mu\text{Ci}/\mu\text{L}$. A minimum of 14 hours is allowed to elapse before proceeding to the next step. The entirety of the solution in the [Ac-225] source

vial is transferred to the “reaction” tube. A minimum of 2 hours is allowed to elapse before the “reaction” tube is assayed and the radioactivity value recorded in unit of μCi .

Preparation of PSMA I&T buffer solution: To a PSMA I&T precursor vial was added Sodium Acetate – Dissolution Buffer (**DB**) to attain a 1 mg/mL solution. The vial is swirled for thirty seconds, inverted several times, until the entire contents are dissolved, and a homogeneous solution is obtained.

Radiolabeling: The PSMA I&T buffer solution described above is transferred to an “intermediate” vial such that the ratio of the volume transferred and the radioactivity in the “reaction” tube is 4.2 $\mu\text{Ci}/\mu\text{L}$. To the “intermediate” vial is added Sodium Acetate – Dissolution Buffer (**DB**) and Sodium Acetate – Sodium Ascorbate Reaction Buffer (**RB**) to attain a mixture that contains equal volumes of **DB** and **RB**, and where the ratio of the total volume in the “intermediate” vial and radioactivity in the “reaction” tube is 2.8 $\mu\text{L}/\mu\text{Ci}$. The entirety of the solution in the “intermediate” vial is transferred to the “reaction” tube. The contents of the “reaction” tube are gently swirled to ensure adequate mixing, before heating on a thermomixer at 90 °C for 15 minutes. Thereafter, the “reaction” tube is transferred to a lead pig and allowed to sit at room temperature for 5-10 minutes.

Final Product formulation: The entire contents of the “reaction” tube are transferred using an appropriately sized syringe to a final product vial labeled as “Ac-225-PSMA-I&T Bulk Product”. To the final product vial was added Ascorbate-DTPA Formulation Buffer using an appropriately sized syringe such that it is 10 times the volume of **RB** and **DB** added in the above step. The solution is slowly and carefully swirled for 30 seconds to ensure that the solution in the “Ac-225- PSMA-I&T Bulk Product” vial is fully mixed.

The “Ac-225- PSMA-I&T Bulk Product” vial is stored in a lead pig labelled “Ac-225-PSMA-I&T Bulk Product Vial” at 2-8 °C for a minimum of 14 hours. The “Ac-225- PSMA-I&T Bulk Product” vial is assayed in the dose calibrator and the radioactivity value of the final product is recorded in unit of μCi .

Table 1 below provides a pharmaceutical composition prepared according to the protocols set forth above.

Table 1. Exemplary formulation of a pharmaceutical composition

Component	Quantity per mL	Function
Ac-225-PSMA-I&T; Total peptide (including metal complexes)	0.85 – 1.26 MBq; 5 – 22 µg	Drug Substance
Water	N/A	Solvent
Sodium Acetate	7.94 mg	Buffer
Sodium L-Ascorbate	52.1 mg	Radioprotectant/Buffer
Diethylenetriaminepentaacetic Acid (DTPA) Pentasodium Salt	52.2 µg	Metal Chelator

Example 2. Evaluation of the Stability of Compositions

The stability of the pharmaceutical composition is evaluated according to the protocol set forth below.

- 5 The bulk final drug product comprising ²²⁵Ac-PSMA-I&T described above is used in a stability test, in a glass container.

The test sample is evaluated for stability by storing upright in a shielded container at the appropriate storage temperature.

The storage location, date and time is recorded corresponding to the batch number.

- 10 Prior to date and time of expiry (7 days from the date of manufacture), the test sample is removed for testing from storage location and allowed to reach room temperature for a minimum of 30 minutes. The sample removal date and time are recorded corresponding to the batch number.

- 15 The temperature monitoring data for the relevant time period of the storage location for the test sample is used to verify that there are no temperature excursions.

The stability of the test sample is evaluated based on the quality attributes shown in Table 2 below.

Table 2. Quality Attributes of the Stability of Pharmaceutical Compositions

Quality Attributes	Method
Appearance	Visual inspection
pH	pH meter
Radioactivity Concentration	Dose calibrator

Chemical content	HPLC-UV
Chemical Purity	HPLC-UV
Radiochemical purity by HPLC	HPLC-gamma counter
Radiochemical impurities by HPLC	HPLC-gamma counter
Radiochemical purity by TLC	TLC-radiometric detector
Sterility	Direct inoculation

To evaluate stability, a pharmaceutical composition was prepared, which had radioactivity of 1.26 mCi, radioactivity concentration of 28 µCi/mL, molar radioactivity of 5.24 µCi/nmol, and radiochemical purity of 99.5%. Following the stability protocol provided above, this pharmaceutical composition exerted stabilities as below as determined by radio thin-layer chromatography (radio-TLC):

The pharmaceutical composition retained 99.0% of intact ²²⁵Ac-PSMA-I&T after 7 days at 2-8 °C.

Provided in Tables 3-6 below include certain pharmaceutical compositions of this disclosure and their stability test. The formulation batches set forth in Tables 4-6 have their compositions covered by Table 3.

Table 3. Exemplary formulations of a pharmaceutical compositions

Ingredient	Concentration
Ac-225- PSMA-I&T	0.85-1.26 MBq/mL
Total peptide (including metal complexes)	5-10 µg/mL
Water	N/A
Hydrochloric Acid (30-35%)	0.14 mg/mL
Sodium Acetate	7.94 mg/mL
Sodium L-Ascorbate	52.1 mg/mL
Diethylenetriaminepentaacetic Acid (DTPA), Pentasodium Salt Solution	52.2 µg/mL

Table 4. Exemplary formulation batches

Batch number	Vial	Volume (mL)	RAC (mCi/mL at TOC)	Orientation ¹	Time Point	Storage Condition	Table
[225Ac]-FPI-2265-23004-ST	20 mL Sterile Vial	2.5	33	Upright	Day 7 + 6 hours	2 – 8°C	Table 4A
[225Ac]-FPI-2265-23005-ST		10	30	Inverted			Table 4B
[225Ac]-FPI-2265-23006-ST		10	30	Upright			Table 4C
[225Ac]-FPI-2265-24007-ST		10	29	Upright			Table 4D

15

Table 4A. Exemplary formulation batch

Process Performance Qualification		PPQ 1	
Batch Number		[225Ac]-FPI-2265-23004-ST	
Stability Sample	Container Closure	20 mL Sterile Vial (SEV20)	
	Orientation	Upright	
	Volume of [225Ac]-FPI-2265 (mL)	2.5 mL	
Test	Acceptance Criteria	Results	
		Day 0 (15-30°C)	Day 7 (2-8°C) + 6 hours (15-30°C)
Radioactivity Concentration at time of calibration (TOC; 12:00 PM, 2 days post end of synthesis)	The radioactivity concentration at TOC must be 23 – 34 $\mu\text{Ci/mL}$ (0.851 – 1.258 MBq/mL)	33 $\mu\text{Ci/mL}$ (1.221 MBq/mL)	33 $\mu\text{Ci/mL}$ (1.221 MBq/mL)
Specific Activity at TOC	The Specific Activity at TOC must be 2.3 – 6.8 $\mu\text{Ci}/\mu\text{g}$ (0.085 – 0.252 MBq/ μg)	4.1 $\mu\text{Ci}/\mu\text{g}$ (0.152 MBq/ μg)	-
Total Peptide Content	The total peptide content must be 5 – 10 $\mu\text{g/mL}$	8 $\mu\text{g/mL}$	8 $\mu\text{g/mL}$
Ascorbate Content	The ascorbate content for ²²⁵ Ac-FPI-2265 Bulk Drug Product must be 38 – 57 mg/mL	47 mg/mL	-
Radiochemical Purity by TLC	% ROI of ²²⁵ Ac-FPI-2265 $\geq 95\%$	99%	99%

Table 4B. Exemplary formulation batch

Process Performance Qualification		PPQ 2	
Batch Number		[225Ac]-FPI-2265-23005-ST	
Stability Sample	Container Closure	20 mL Sterile Vial (SEV20)	
	Orientation	Inverted	
	Volume of [225Ac]-FPI-2265 (mL)	10 mL	
Specification	Acceptance Criteria	Results	
		Day 0 (15-30°C)	Day 7 (2-8°C) + 6 hours (15-30°C)
Radioactivity Concentration at TOC	The radioactivity concentration at TOC must be 23 – 34 $\mu\text{Ci/mL}$ (0.851 – 1.258 MBq/mL)	29 $\mu\text{Ci/mL}$ (1.073 MBq/mL)	30 $\mu\text{Ci/mL}$ (1.110 MBq/mL)
Specific Activity at TOC	The Specific Activity at TOC must be 2.3 – 6.8 $\mu\text{Ci}/\mu\text{g}$ (0.085 – 0.252 MBq/ μg)	3.6 $\mu\text{Ci}/\mu\text{g}$ (0.133 MBq/ μg)	-
Total Peptide Content	The total peptide content must be 5 – 10 $\mu\text{g/mL}$	8 $\mu\text{g/mL}$	7 $\mu\text{g/mL}$

Ascorbate Content	The ascorbate content for ²²⁵ Ac-FPI-2265 Bulk Drug Product must be 38 – 57 mg/mL	47 mg/mL	-
Radiochemical Purity by TLC	% ROI of ²²⁵ Ac-FPI-2265 ≥ 95%	100%	99%

Table 4C. Exemplary formulation batch

Process Performance Qualification		PPQ 3	
Batch Number		[²²⁵ Ac]-FPI-2265-23006-ST	
Stability Sample	Container Closure	20 mL Sterile Vial (SEV20)	
	Orientation	Upright	
	Volume of [²²⁵ Ac]-FPI-2265 (mL)	10 mL	
Specification	Acceptance Criteria	Results	
		Day 0 (15-30°C)	Day 7 (2-8°C) + 6 hours (15-30°C)
Radioactivity Concentration at TOC	The radioactivity concentration at TOC must be 23 – 34 µCi/mL (0.851 – 1.258 MBq/mL)	31 µCi/mL (1.147 MBq/mL)	30 µCi/mL (1.110 MBq/mL)
Specific Activity at TOC	The Specific Activity at TOC must be 2.3 – 6.8 µCi/µg (0.085 – 0.252 MBq/µg)	4.4 µCi/µg (0.163 MBq/µg)	-
Total Peptide Content	The total peptide content must be 5 – 10 µg/mL	7 µg/mL	7 µg/mL
Ascorbate Content	The ascorbate content for ²²⁵ Ac-FPI-2265 Bulk Drug Product must be 38 – 57 mg/mL	47 mg/mL	-
Radiochemical Purity by TLC	% ROI of ²²⁵ Ac-FPI-2265 ≥ 95%	99%	99%

5

10

Table 4D. Exemplary formulation batch

Process Performance Qualification		PPQ 4	
Batch Number		[225Ac]-FPI-2265-24007-ST	
Stability Sample	Container Closure	20 mL Sterile Vial (SEV20)	
	Orientation	Upright	
	Volume of [225Ac]-FPI-2265 (mL)	10 mL	
Specification	Acceptance Criteria	Results	
		Day 0 (15-30°C)	Day 7 (2-8°C) + 6 hours (15-30°C)
Radioactivity Concentration at TOC	The radioactivity concentration at TOC must be 23 – 34 µCi/mL (0.851 – 1.258 MBq/mL)	30 µCi/mL (1.11 MBq/mL)	29 µCi/mL (1.073 MBq/mL)
Total Peptide Content	The total peptide content must be 5 – 10 µg/mL	8 µg/mL	7 µg/mL
Ascorbate Content	The ascorbate content for ²²⁵ Ac-FPI-2265 Bulk Drug Product must be 38 – 57 mg/mL	47 mg/mL	-
Radiochemical Purity by TLC	% ROI of ²²⁵ Ac-FPI-2265 ≥ 95%	100%	100%

Table 5. Stability Results for [225Ac]-FPI-2265 Process Performance Qualification Batch
[225Ac]-FPI-2265-24024-ST (PPQ5)

Process Performance Qualification		PPQ 5	
Batch Number		[225Ac]-FPI-2265-24024-ST	
Stability Sample	Container Closure	20 mL Sterile Vial (SEV20)	
	Orientation	Inverted	
	Volume of [225Ac]-FPI-2265 (mL)	5.5 mL	
Specification	Acceptance Criteria	Results	
		Day 0 (15-30°C)	Day 7 (2-8°C) + 6 hours (15-30°C)
Visual Inspection	A clear, colorless to slightly yellow solution, free of visible particulates.	Conforms	Conforms

Process Performance Qualification		PPQ 5	
Batch Number		[225Ac]-FPI-2265-24024-ST	
Stability Sample	Container Closure	20 mL Sterile Vial (SEV20)	
	Orientation	Inverted	
	Volume of [225Ac]-FPI-2265 (mL)	5.5 mL	
Specification	Acceptance Criteria	Results	
		Day 0 (15-30°C)	Day 7 (2-8°C) + 6 hours (15-30°C)
Radionuclidic Identity	Main gamma emission present at 117 ± 1 keV, 188 ± 1 keV, 218 ± 1 keV, and 441 ± 1 keV.	Conforms	-
Radionuclidic Purity	Radionuclidic Purity must be $\geq 99\%$	Conforms	-
pH	The measured pH must be between 6.0 – 8.0	6.6	6.4
Filter Integrity Test	The measured bubble point must be ≥ 50 psi as per manufacturer specifications	70 psi	-
Bacterial Endotoxin	The Bacterial Endotoxin content of a patient dose must be ≤ 8.75 EU/mL	≤ 5.00 EU/mL	-
Radioactivity Concentration at TOC	The radioactivity concentration at TOC must be 23 – 34 $\mu\text{Ci/mL}$ (0.851 – 1.258 MBq/mL)	29 $\mu\text{Ci/mL}$ (1.073 MBq/mL)	29 $\mu\text{Ci/mL}$ (1.073 MBq/mL)
Specific Activity at TOC	The Specific Activity at TOC must be 1.0 – 6.8 $\mu\text{Ci}/\mu\text{g}$ (0.037 – 0.252 MBq/ μg)	1.6 $\mu\text{Ci}/\mu\text{g}$ (0.059 MBq/ μg)	-
Chemical Purity	The Chemical Purity must be $\geq 90\%$	100%	100%
Radiochemical Identity	The RRT of the [225Ac]-FPI-2265 fraction collected peak in the sample injection to the FPI-2661 peak in the UV channel of the FPI-2661 reference standard injection must be 90 – 110%	100%	-
Radiochemical Purity by HPLC	% ROI of 225Ac-FPI-2265 $\geq 90\%$	93%	91%
	Total Radiochemical Impurities $\leq 10\%$	1%	2%
	Largest Radiochemical Impurity $\leq 5\%$	0%	1%
Total Peptide Content	The total peptide content must be 5 – 22 $\mu\text{g/mL}$	19 $\mu\text{g/mL}$	17 $\mu\text{g/mL}$

Process Performance Qualification		PPQ 5	
Batch Number		[225Ac]-FPI-2265-24024-ST	
Stability Sample	Container Closure	20 mL Sterile Vial (SEV20)	
	Orientation	Inverted	
	Volume of [225Ac]-FPI-2265 (mL)	5.5 mL	
Specification	Acceptance Criteria	Results	
		Day 0 (15-30°C)	Day 7 (2-8°C) + 6 hours (15-30°C)
Ascorbate Content	The ascorbate content for ²²⁵ Ac-FPI-2265 Bulk Drug Product must be 38 – 57 mg/mL	47 mg/mL	-
Radiochemical Purity by TLC	% ROI of ²²⁵ Ac-FPI-2265 ≥ 95%	100%	100%
Sterility	No microbial growth observed on sample media at the completion of not less than 14-day incubation	No growth	-

Table 6. Stability testing at 7 and 14 days with storage 2-8 °C

Batch ID	A65124IN23A		
Heating time (step B in embodiment)	14 min		
	T0	T+7 days	T+14 days
Radioactivity concentration at TOC	26.74 µCi/mL	26.74 µCi/mL	26.74 µCi/mL
Ascorbate Content	45.1 mg/mL	-	-
Radiochemical Purity by TLC (%)	99	99	97.7
Batch ID	A65089IN23A		
Heating time (step B in embodiment)	15 min		
	T0	T+7 days	T+14 days
Radioactivity concentration at TOC	27.44 µCi/mL	27.44 µCi/mL	27.44 µCi/mL
Ascorbate Content	47 mg/mL	-	-
Radiochemical Purity by TLC (%)	99	97	96

Example 3. Administration of Compositions in Treatment of Cancer

The pharmaceutical composition comprising ^{225}Ac -radioconjugate is administered to patient having PSMA expressing cancer according to the protocols set forth below.

5 *Dose Preparation*

Each dose is individually prepared prior to dosing. The dose calibrator used for participant administration measurement should be the same machine that is utilized during the dose calibrator calibration process during study start-up.

10 Dose is prepared aseptically for administration under site's standard environmental conditions and standard operating procedures (SOPS). The below procedures are followed for preparing for administration: The vial containing the investigational medicinal product (IMP) is allowed in the lead pig to thaw on the bench at room temperature. Thaw time is estimated to take 1 hour, but sites can use their own judgement when thawing to ensure the IMP has come to room temperature prior to administration.

15 The area of preparation is ensured to be clean prior to dispensing. Prior to donning gloves, operator hands shall be washed or sanitized using an alcohol-based hand sanitizer. Once gloves are donned, it is recommended that they are sprayed with 70% isopropyl alcohol (IPA). The vial septum shall be wiped with a sterile IPA pad. The wiped septum is allowed to dry before piercing the septum.

20 A sterile disposable syringe and needle shall be used to prepare the injection and shall be assembled immediately before preparing the injection. Syringes shall be assembled with needles in a clean environment (or aseptic environment if possible). Aseptic connections shall not be handled directly.

25 Radioactivity concentration of the product at the time of calibration (TOC). TOC is the date and time when the supplied radionuclide corresponds to the stated activity of the radionuclide. After the TOC, the radioactivity is decreased. The radioactivity concentration, and time and date of calibration, are stated on the Certificate of Analysis (CoA). Decay correction factor ^{225}Ac is used to correct for physical decay to the nearest hour.

30 For [225Ac]-PSMA-I&T administration, the actual body weight from the participant's general screening visit shall be used to calculate the [225Ac]-PSMA-I&T dose.

The estimated volume of [225Ac]-PSMA-I&T to be administered to a participant in need thereof is calculated as follows:

$$\text{Volume (mL)} = [\text{Dose Level (kBq/kg)} \times \text{Body weight in kg}] / [\text{Decay Correction Factor Ac-225} \times \text{Activity Concentration at TOC (kBq/mL)}]$$

5

Dose Administration

Administration of the pharmaceutical composition follows the below procedures for administering [225Ac]-PSMA-I&T to the participant.

10 The IMP should not be diluted or administered with any other IV fluids, combined with other drugs, or administered through an infusion set used at the same time for any purpose other than the current IMP administration.

The IMP is administered by slow intravenous injection (IV, 2-5 minutes). For [225Ac]-PSMA-I&T, the dose to be administered depends on participant weight and study cohort assignment.

15 The injection may be administered via a peripheral vein (preferred) or a central vein. The use of a 3-way stopcock is recommended during injection to ensure intravenous delivery of the products and to ensure proper priming and flushing. After administration, the line will be thoroughly flushed with normal saline to ensure delivery of full dose.

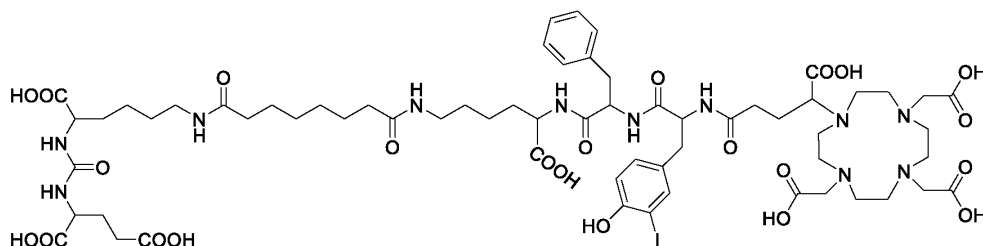
20 Following administration, the injection line should be removed from the participant and not used for any other procedures. The syringe and all contaminated tubing should be assayed in the same dose calibrator to determine the net dose administered. The volume injected, time of administration, and participant net dose should be recorded.

OTHER EMBODIMENTS

25 Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments described herein. Such equivalents are intended to be encompassed by the following claims.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition, comprising:
 - (a) an ^{225}Ac -radioconjugate or a pharmaceutically acceptable salt thereof, wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with a compound of Formula I, or a prodrug thereof:

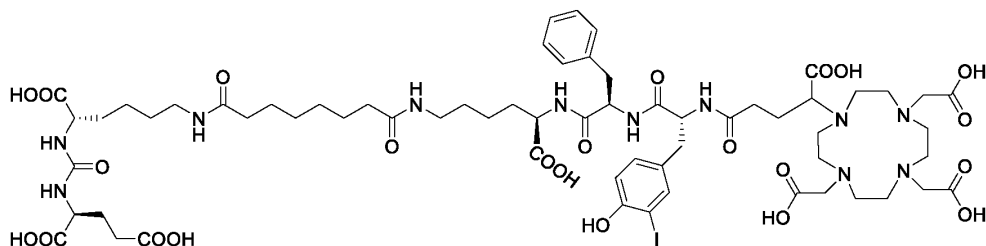


(I),

wherein the ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof is present in the pharmaceutical composition at a concentration of about 1 $\mu\text{g/mL}$ to about 100 $\mu\text{g/mL}$, or in an amount that provides a radioactivity concentration of about 10 $\mu\text{Ci/mL}$ to about 1000 $\mu\text{Ci/mL}$ of the pharmaceutical composition;

- (b) sodium acetate, wherein the sodium acetate is present in the pharmaceutical composition at a concentration of about 1 mg/mL to about 400 mg/mL ,
 - (c) sodium L-ascorbate, wherein the sodium L-ascorbate is present in the pharmaceutical composition at a concentration of about 40 mg/mL to about 150 mg/mL ; and
 - (d) diethylenetriamine pentaacetate (DTPA), wherein the DTPA is present in the pharmaceutical composition at a concentration of about 5 $\mu\text{g/mL}$ to about 60 $\mu\text{g/mL}$,
- wherein the pharmaceutical composition is an aqueous formulation and is free of a gentisate compound.

2. The pharmaceutical composition of claim 1, wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure:



3. The pharmaceutical composition of claim 1, wherein the ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof is present in the pharmaceutical composition at a concentration of about 7 $\mu\text{g/mL}$ to about 9 $\mu\text{g/mL}$.

4. The pharmaceutical composition of claim 1, wherein the sodium acetate is present in the pharmaceutical composition at a concentration of about 6 mg/mL to about 10 mg/mL.

5. The pharmaceutical composition of claim 1, wherein the sodium L-ascorbate is present in the pharmaceutical composition at a concentration of about 50 mg/mL.

6. The pharmaceutical composition of claim 1, wherein the DTPA is present in the pharmaceutical composition at a concentration of about 50 $\mu\text{g/mL}$.

7. The pharmaceutical composition of claim 1, wherein the composition has a pH of between 3 and 9.

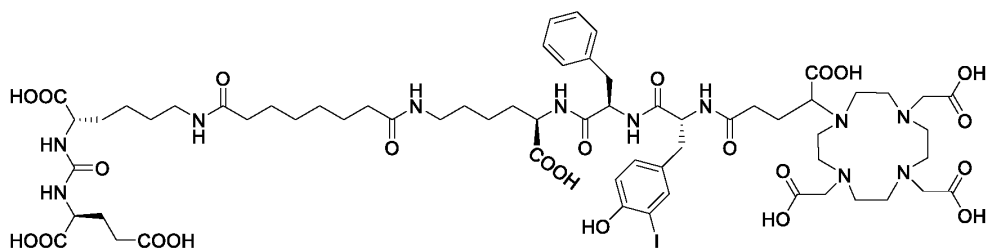
8. The pharmaceutical composition of claim 1, wherein the composition further comprises ethanol, wherein the ethanol is present in the pharmaceutical composition at a concentration of less than 40 mg/mL or about 40 mg/mL to about 100 mg/mL.

9. The pharmaceutical composition of claim 1, wherein the composition is free of ethanol.

10. The pharmaceutical composition of claim 1, comprising:

(a) ^{225}Ac -radioconjugate or a pharmaceutically acceptable salt thereof,

wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure:



wherein the ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof is present in the pharmaceutical composition at a concentration of 7-9 $\mu\text{g/mL}$;

(b) sodium acetate present in the pharmaceutical composition at a concentration of 7-8 mg/mL,

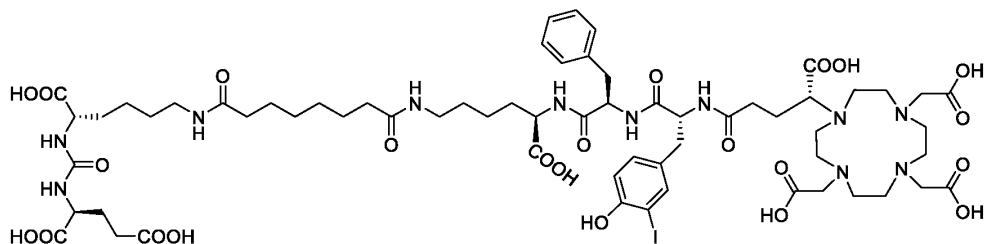
(c) sodium L-ascorbate present in the pharmaceutical composition at a concentration of 51-54 mg/mL; and

(d) diethylenetriamine pentaacetate (DTPA), wherein the DTPA is diethylenetriaminepentaacetic acid pentasodium salt, present in the pharmaceutical composition at a concentration of 51-54 $\mu\text{g/mL}$.

11. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition retains at least 95% of said ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof after 72 hours at about 2 °C to about 25 °C as determined by radio thin-layer chromatography (radio-TLC).

12. The pharmaceutical composition of claim 11, wherein the pharmaceutical composition retains at least 95% of said ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof after 7-10 days at about 2 °C to about 25 °C as determined by radio-TLC.

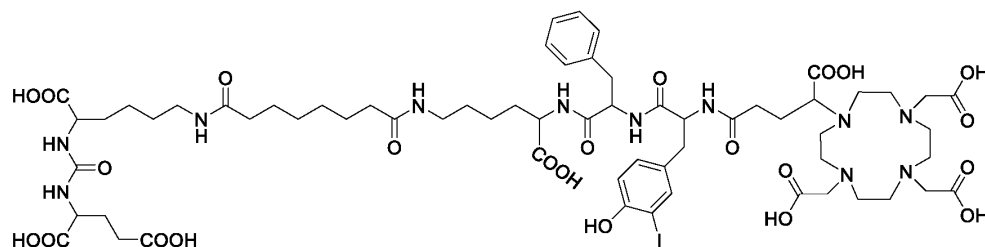
13. The pharmaceutical composition of claim 1, wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure:



14. A pharmaceutical composition, consisting essentially of:

(a) an ^{225}Ac -radioconjugate or a pharmaceutically acceptable salt thereof,

wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with a compound of Formula I, or a prodrug thereof:



(I),

wherein the ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof is present in the pharmaceutical composition at a concentration of about 1 $\mu\text{g/mL}$ to about 100 $\mu\text{g/mL}$, or in an amount that provides a radioactivity concentration of about 10 $\mu\text{Ci/mL}$ to about 1000 $\mu\text{Ci/mL}$ of the pharmaceutical composition;

(b) sodium acetate, wherein the sodium acetate is present in the pharmaceutical composition at a concentration of about 1 mg/mL to about 400 mg/mL ,

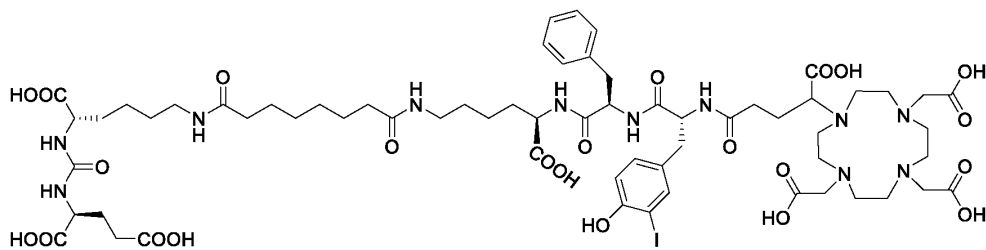
(c) sodium L-ascorbate, wherein the sodium L-ascorbate is present in the pharmaceutical composition at a concentration of about 40 mg/mL to about 150 mg/mL ; and

(d) diethylenetriamine pentaacetate (DTPA), wherein the DTPA is present in the pharmaceutical composition at a concentration of about 5 $\mu\text{g/mL}$ to about 60 $\mu\text{g/mL}$,

wherein the pharmaceutical composition is an aqueous formulation and is free of a gentisate compound.

15. The pharmaceutical composition of claim 14, wherein:

(a) said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with the following structure:



wherein the ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof is present in the pharmaceutical composition at a concentration of 7-9 $\mu\text{g/mL}$;

(b) said sodium acetate is present in the pharmaceutical composition at a concentration of 7-8 mg/mL,

(c) said sodium L-ascorbate is present in the pharmaceutical composition at a concentration of 51-54 mg/mL; and

(d) said DTPA is diethylenetriaminepentaacetic acid pentasodium salt, present in the pharmaceutical composition at a concentration of 51-54 $\mu\text{g/mL}$.

16. A method for treating a patient having cancer expressing Prostate Specific Membrane Antigen (PSMA), wherein the method comprises administering to the patient in need thereof a therapeutically effective amount of a pharmaceutical composition of claim 1 or 14.

17. The method of claim 16, wherein the PSMA expressing cancer is selected from the group consisting of prostate cancer, breast cancer, colorectal cancer, renal cell cancer, bladder cancer, testicular cancer, neuroendocrine cancer, and brain tumor.

18. A method for preparing an ^{225}Ac -PSMA I&T composition, comprising:

(a) radiolabeling PSMA I&T with ^{225}Ac in a reaction buffer solution in the absence of a gentisate compound, wherein the reaction buffer solution comprises sodium acetate and sodium L-ascorbate;

(b) heating the mixture from step (a) for a pre-determined time to form a radiolabeled product; and

(c) mixing the radiolabeled product with a formulation buffer solution to form an ^{225}Ac -PSMA I&T composition, wherein the formulation buffer solution comprises sodium L-ascorbate and diethylenetriaminepentaacetic acid pentasodium salt.

19. The method of claim 18, wherein the gentisate compound is gentisic acid.

20. The method of claim 18, wherein the pre-determined time is less than 25 minutes.

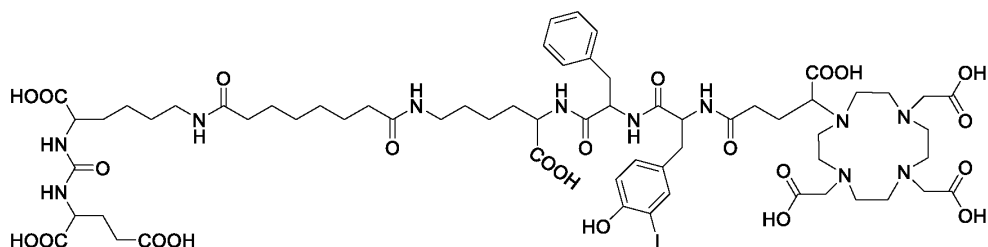
21. The method of claim 18, wherein said ^{225}Ac is reconstituted in an HCl solution having a concentration of less than 0.05 M.

22. The method of claim 18, wherein the ^{225}Ac -PSMA I&T composition is free of a gentisate compound and retains intact at least 99% of ^{225}Ac -PSMA I&T for 7 days or longer at about 2 °C to about 8 °C as determined by radio-TLC.

23. A pharmaceutical composition, comprising:

(b) an ^{225}Ac -radioconjugate or a pharmaceutically acceptable salt thereof,

wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with a compound of Formula I, or a prodrug thereof:



(I),

wherein the ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof is present in the pharmaceutical composition at a concentration of about 1 $\mu\text{g/mL}$ to about 100 $\mu\text{g/mL}$, or in an amount that provides a radioactivity concentration of about 10 $\mu\text{Ci/mL}$ to about 1000 $\mu\text{Ci/mL}$ of the pharmaceutical composition;

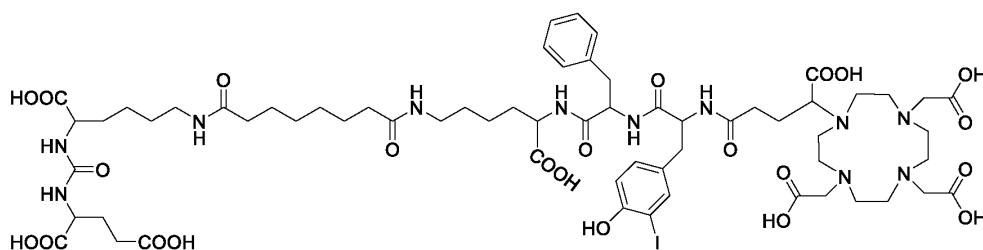
(b) sodium acetate, wherein the sodium acetate is present in the pharmaceutical composition at a concentration of about 1 mg/mL to about 400 mg/mL,

(c) sodium L-ascorbate, wherein the sodium L-ascorbate is present in the pharmaceutical composition at a concentration of about 40 mg/mL to about 150 mg/mL; and

(d) diethylenetriamine pentaacetate (DTPA), wherein the DTPA is present in the pharmaceutical composition at a concentration of about 5 µg/mL to about 60 µg/mL, wherein the pharmaceutical composition is an aqueous formulation and is substantially free of a gentisate compound.

24. A pharmaceutical composition, consisting essentially of:

(b) an ^{225}Ac -radioconjugate or a pharmaceutically acceptable salt thereof, wherein said ^{225}Ac -radioconjugate comprises ^{225}Ac chelated with a compound of Formula I, or a prodrug thereof:



(I),

wherein the ^{225}Ac -radioconjugate or the pharmaceutically acceptable salt thereof is present in the pharmaceutical composition at a concentration of about 1 µg/mL to about 100 µg/mL, or in an amount that provides a radioactivity concentration of about 10 µCi/mL to about 1000 µCi/mL of the pharmaceutical composition;

(b) sodium acetate, wherein the sodium acetate is present in the pharmaceutical composition at a concentration of about 1 mg/mL to about 400 mg/mL,

(c) sodium L-ascorbate, wherein the sodium L-ascorbate is present in the pharmaceutical composition at a concentration of about 40 mg/mL to about 150 mg/mL; and

(d) diethylenetriamine pentaacetate (DTPA), wherein the DTPA is present in the pharmaceutical composition at a concentration of about 5 µg/mL to about 60 µg/mL, wherein the pharmaceutical composition is an aqueous formulation and is substantially free of a gentisate compound.

25. The method of claim 18, wherein the ^{225}Ac -PSMA I&T composition is substantially free of a gentisate compound and retains intact at least 99% of ^{225}Ac -PSMA I&T for 7 days or longer at about 2 °C to about 8 °C as determined by radio-TLC.