

STABILIZED COMPOSITIONS OF RADIONUCLIDES AND USES THEREOF**CROSS REFERENCE TO RELATED APPLICATIONS**

[001] This application claims the benefit of U.S. Provisional Application No. 63/228,535, filed on August 2, 2021; U.S. Provisional Application No. 63/329,306, filed on April 8, 2022; and is a continuation-in-part of U.S. Application No. 17/665,202, filed on February 4, 2022; each of which is incorporated herein by reference in its entirety.

SEQUENCE LISTING

[002] The instant application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML file, created on August 1, 2022, is named 59541-718_601_SL.xml and is 155,726 bytes in size.

BACKGROUND

[003] In the United States, cancer is the leading cause of death for those under 65 years of age, and it accounted for about 21% of all deaths in 2018. Neuroendocrine tumors (NETs) arise from neuroendocrine cells and most commonly develop in the lung, digestive tract and pancreas. NETs are one of the cancers that need systemic therapies because either they are inoperable, or they are diagnosed at an advanced stage with distant spread of tumor cells. Traditional radiotherapies such as external beam radiation therapy have been used for decades as a standard-of-care treatment for diagnosed cancer patients. While some patients respond to external beam radiation therapy, many others do not. Further, metastasis and circulating tumor cells can spread and remain in the bloodstream or bodily fluids after standard-of-care treatment and lead to resistance to therapy. The presence of cancer cells in various parts of the body reduces the therapeutic efficacy of traditional radiotherapies. Accordingly, strategies for targeted radiotherapies are being developed for better cancer treatment and diagnosis. One of the major challenges in the production of radiopharmaceutical drugs is to extend the shelf-life of product to allow treatment of patients at remote locations from the manufacturer site. There remains a need for compositions of radionuclides, e.g., alpha-particle emitting radionuclides, that have improved stability and shelf lives.

SUMMARY

[004] One of the major challenges in the production of radiopharmaceutical drugs is to extend the shelf-life of product to allow treatment of patients at remote locations from the manufacturer site. As radionuclides, such as Actinium-225, decay, a series of highly reactive chemicals are generated. In some cases, they can react with the drug substance, e.g., causing degradation of the

radioisotope-containing drug and increasing radioactive impurity overtime. In one aspect, provided herein are liquid radiopharmaceutical formulations that provide enhanced stability for alpha-emitting radionuclide such as Actinium-225. In one aspect, provided herein are liquid radiopharmaceutical formulations comprising ^{225}Ac -DOTA-TATE that are stable for at least 120 hours.

[005] In one aspect, provided herein is a liquid radiopharmaceutical composition comprising: (i) a conjugate, wherein the conjugate is ^{225}Ac -DOTA-TATE; (ii) one or more stabilizing agents; and (iii) an aqueous vehicle. In one aspect, provided herein is a liquid radiopharmaceutical composition comprising: (i) a conjugate, wherein the conjugate is ^{225}Ac -DOTA-TOC; (ii) one or more stabilizing agents; and (iii) an aqueous vehicle. In one aspect, the present disclosure relates to a liquid radiopharmaceutical composition comprising, a conjugate, optionally one or more stabilizing agents, and an aqueous vehicle. The conjugate further comprises a targeting ligand, a metal chelator covalently attached to the targeting ligand, and a radionuclide that is bound to the metal chelator. In some embodiments, the targeting ligand binds to a somatostatin receptor (SSR), such as a somatostatin receptor type 1 (SSTR1), somatostatin receptor type 2 (SSTR2), somatostatin receptor type 3 (SSTR3), somatostatin receptor type 4 (SSTR4), and/or somatostatin receptor type 5 (SSTR5). In some embodiments, the targeting ligand binds to a somatostatin receptor type 2 (SSTR2). In some embodiments, the targeting ligand is a binding peptide, which comprises 6 to 14 amino acid residues. In some embodiments, the binding peptide comprises an amino acid sequence with at least 90% identity to a sequence selected from SEQ IDs 1 to 96. In some embodiments, the binding peptide comprises an amino acid sequence selected from SEQ IDs 1 to 96. In some embodiments, the targeting ligand is octreotate, octreotide, D-Phe¹-cyclo(Cys²-Tyr³-D-Trp⁴-Lys⁵-Thr⁶-Cys⁷)Thr⁸ (SEQ ID NO: 97) (tyr³-octreotate or TATE), D-Phe¹-cyclo(Cys²-Tyr³-D-Trp⁴-Lys⁵-Thr⁶-Cys⁷)Thr(ol)⁸ (SEQ ID NO: 98) (Phe¹-Tyr³octreotide, edotreotide, or TOC), D-Phe¹-cyclo(Cys²-Phe³-D-Trp⁴-Lys⁵-Thr⁶-Cys⁷)Thr(ol)⁸ (SEQ ID NO: 99) (OC), D-Phe¹-cyclo(Cys²-1-Nal-D-Trp⁴-Lys⁵-Thr⁶-Cys⁷)Thr(ol)⁸ (SEQ ID NO: 100) (NOC), p-Cl-Phe-cyclo(D-Cys-Aph(Hor)-D-Aph(Cbm)-Lys-Thr-Cys)-D-Tyr-NH₂ (SEQ ID NO: 101) (JR11), or p-Cl-Phe-cyclo(D-Cys-Tyr-D-Aph(Cbm)-Lys-Thr-Cys)-D-Tyr-NH₂ (SEQ ID NO: 102) (LM3). In some embodiments, the targeting ligand is tyr³-octreotate, edotreotide, octreotate, or octreotide. In some embodiments, the targeting ligand is tyr³-octreotate. In some embodiments, the targeting ligand is an agonist of the SSR. In some embodiments, the targeting ligand is an antagonist of the SSR. In another embodiment, the targeting ligand is a small molecule compound, such as L-797,591, L-779,976, L-796,778, L-803,087, or L-817,818. In some embodiments, a binding affinity of the targeting ligand to a human SSR is not more than 250 nM, not more than 100 nM, not more than 50 nM, or not more

than 5 nM, as determined by half maximal inhibitory concentration (IC_{50}). In some embodiments, the binding affinity of the targeting ligand to a human SSR is not more than 250 nM, as determined by half maximal inhibitory concentration (IC_{50}). In some embodiments, the binding affinity of the targeting ligand to a human SSR is not more than 100 nM, as determined by half maximal inhibitory concentration (IC_{50}). In some embodiments, the binding affinity of the targeting ligand to a human SSR is not more than 50 nM, as determined by half maximal inhibitory concentration (IC_{50}). In some embodiments, the binding affinity of the targeting ligand to a human SSR is not more than 5 nM, as determined by half maximal inhibitory concentration (IC_{50}). In some embodiments, the binding affinity of the targeting ligand to a human SSR is not more than 2 nM, as determined by half maximal inhibitory concentration (IC_{50}). In some embodiments, the human SSR is SSTR2. In some embodiments, the targeting ligand is covalently linked to the metal chelator through a linker. In some embodiments, the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content bound as part of the conjugate after 72 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC). In some embodiments, the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content bound as part of the conjugate after 120 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC). In some embodiments, the radiopharmaceutical composition retains at least 95 % of the ^{225}Ac content bound as part of the conjugate after 120 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC). In some embodiments, the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content bound as part of the conjugate after 120 hours at about 20°C to about 25°C as determined by high performance liquid chromatography/fraction collection (HPLC-FC). In some embodiments, the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content bound as part of the conjugate after 72 hours at about 20°C to about 25°C as determined by high performance liquid chromatography/fraction collection (HPLC-FC).

[006] In one aspect, described herein is a radiopharmaceutical composition comprising a conjugate that further comprises a targeting ligand that covalently links to a metal chelator through a linker. In some embodiments, the metal chelator is selected from AAZTA, BAT, BAT-TM, Crown, Cyclen, DO2A, CB-DO2A, DO3A, H3HP-DO3A, Oxo-DO3A, p-NH₂-Bn-Oxo-DO3A, DOTA, DOTA-3py, DOTA-PA, DOTA-GA, DOTA-4AMP, DOTA-2py, DOTA-1py, p-SCN-Bn-DOTA, CHX-A''-EDTA, MeO-DOTA-NCS EDTA, DOTAMAP, DOTAGA, DOTAGA-anhydride, DOTMA, DOTASA, DOTAM, DOTP, CB-Cyclam, TE2A, CB-TE2A, CB-TE2P, DM-TE2A, MM-TE2A, NOTA, NOTP, HEHA, HEHA-NCS, p-SCN-Bn-HEHA, DTPA, CHX-A''-DTPA, p-NH₂-Bn-CHX-A''-DTPA, p-SCN-DTPA, p-SCN-Bz-Mx-DTPA, 1B4M-DTPA-

DTPA, p-SCN-Bn1B-DTPA, p-SCN-Bn-1B4M-DTPA, p-SCN-Bn-CHX-A"-DTPA, PEPA, p-SCN-Bn-PEPA, 1,4,8,11-tetraazacyclo tetradecane-1,4,8,11-tetrapropionic acid (TETPA), DOTPA, DOTMP, DOTPM, t-Bu-calix[4]arene-tetracarboxylic acid, macropa, macropa-NCS, macropid, H₃L¹, H₃L⁴, H₂azapa, H₅decapa, bispa², H₄pypa, H₄octapa, H₄CHXoctapa, p-SCN-Bn-H₄octapa, p-SCN-Bn-H₄octapa, TTHA, p-NO₂-Bn-neunpa, H₄octox, H₂macropa, H₂bispa², H₄phospa, H₆phospa, p-SCN-Bn-H₆phospa, TETA, p-NO₂-Bn-TETA, TRAP, TRAP-Pr, TPA, HBED, SHBED, HBED-CC, (HBED-CC)TFP, DMSA, DMPS, DHLA, lipoic acid, TGA, BAL, Bis-thioseminarabazones, p-SCN-NOTA, nNOTA, NODAGA, CB-TE1A1P, 3P-C-NETA-NCS, 3p-C-DEPA, 3P-C-DEPA-NCS, TCMC, PCTA, NODIA-Me, TACN, pycup1A1B, pycup2A, THP, DEDPA, H₂DEDPA, p-SCN-Bn-H₂DEDPA, p-SCN-Bn-TCMC, motexafin, NTA, NOC, 3p-C-NETA, p-NH₂-Bn-TE3A, SarAr, DiAmSar, SarAr-NCS, AmBaSar, BaBaSar, TACN-TM, CP256, C-NE3TA, C-NE3TA-NCS, NODASA, NETA-monoamide, C-NETA, TACN-HSB, NOPO, BPCA, p-SCN-Bn-DRO, DRO-ChX-Mal, DFO, DFO-IAC, DFO-BAC, DiP-LICAM, EC, SBAD, BAPEN, TACHPYR, NEC-SP, L^{py}, L1, L2, L3, and EuK-106. In another embodiment, the metal chelator is a metal chelator illustrated in FIG. 3 to FIG. 17. In some embodiments, the metal chelator is DOTA, HEHA, or macropa. The metal chelator can be DOTA.

[007] In one aspect, the disclosure described herein is a radiopharmaceutical composition comprising one or more stabilizing agents. The stabilizing agent can comprise a radiolysis stabilizer, which can be an amino acid or a peptide or a derivative thereof, a vitamin or a derivative thereof, a lipid or a derivative thereof, a carbohydrate or a derivative thereof, a volume expander or an antioxidant. In some embodiments, the amino acid or peptide is selected from N-Acetyl-L-cysteine, Glutathione, L-Lysine, Selenol-L-methionine, Glutathione, Albumin, Melatonin, Taurine, Alanine, Arginine, Asparagine, Aspartic acid, Cysteine, Glutamine, Glutamic acid, Glycine, Histidine, Isoleucine, Lysine, Methionine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, Valine, and derivatives thereof. In some embodiments, the amino acid is Methionine. In some embodiments, the radiolysis stabilizer is an antioxidant, such as a flavonoid or a derivative thereof. In some embodiments, the flavonoid is (2S,3R)-2-(3,4-Dihydroxyphenyl)-3,4-dihydro-1(2H)-benzopyran-3,5,7-triol 3-(3,4,5-trihydroxybenzoate ((-) Catechin gallate or CG), 3,3',4',5,5',7-Hexahydroxyflavylium chloride, (-)-cis-3,3',4',5,7-Pentahydroxyflavane (Epi-Catechin or EC), 7-Hydroxy-3-(4'-methoxyphenyl)-4H-benzopyran-4-one, 3,4,5-Trihydroxybenzoic acid (Gallic acid), 3,4',5,7-Tetrahydroxyflavone (Kaempferol), Luteolin, 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxochromen-4-one (Rutin hydrate), Quercetin, (2R,3R)-5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-3-yl 3,4,5-trihydroxybenzoate (EpiGallo-Catechin gallate or EGCg), (2R,3R)-

2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3,4-dihydro-2H-chromen-3-yl] 3,4,5-trihydroxybenzoate or Epi-Catechin Gallate (ECG), (2R,3R)-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol (Epigallo-Catechin or EGC), or (2R,3S)-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol (Gallo-Catechin or GC). In some embodiments, the flavonoid is a catechin or a derivative thereof, for example, (2S,3R)-2-(3,4-Dihydroxyphenyl)-3,4-dihydro-1(2H)-benzopyran-3,5,7-triol 3-(3,4,5-trihydroxybenzoate ((-) Catechin gallate or CG), (-)-cis-3,3',4',5,7-Pentahydroxyflavane (Epi-Catechin or EC), 3,4,5-Trihydroxybenzoic acid (Gallic acid), (2R,3R)-5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-3-yl 3,4,5-trihydroxybenzoate (EpiGallo-Catechin gallate or EGCg), (2R,3R)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3,4-dihydro-2H-chromen-3-yl] 3,4,5-trihydroxybenzoate or Epi-Catechin Gallate (ECG), (2R,3R)-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol (Epigallo-Catechin or EGC), or (2R,3S)-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol (Gallo-Catechin or GC). The antioxidant can also be a carotenoid or a derivative thereof, such as all-trans-Fucoxanthin, Lycopene, Xanthophyll, Beta carotene, Lycopene, or Lutein. In some embodiments, the antioxidant is N-acetyl cysteine, L-Ascorbic acid, N-tert-Butyl- α -phenylnitron, 3-(3,4-Dihydroxyphenyl)-2-propenoic acid (Caffeic Acid), β -Carotene, Provitamin A, (2S,3R)-2-(3,4-Dihydroxyphenyl)-3,4-dihydro-1(2H)-benzopyran-3,5,7-triol 3-(3,4,5-trihydroxybenzoate ((-) Catechin gallate or CG), 1,4,5-Trihydroxycyclohexanecarboxylic acid, trans-4-Hydroxycinnamic acid (p-Coumaric acid), 3,3',4',5,5',7-Hexahydroxyflavylium chloride, Thiocytic Acid (Dihydrolipoic Acid, DHLA), 4,4',5,5',6,6'-Hexahydroxydiphenic acid 2,6,2',6'-dilactone (Ellagic acid), (-)-cis-3,3',4',5,7-Pentahydroxyflavane (Epi-Catechin or EC), 2-Methoxy-4-(2-propenyl) phenol, trans-4-Hydroxy-3-methoxycinnamic acid (Ferulic acid), 7-Hydroxy-3-(4'-methoxyphenyl)-4H-benzopyran-4-one, all-trans-Fucoxanthin, 3,4,5-Trihydroxybenzoic acid (Gallic acid), (2S,3R)-2-(3,4,5-Trihydroxyphenyl)-3,4-dihydro-1(2H)-benzopyran-3,5,7-triol ((-)Gallocatechin), Glutathione, 2-(3,4-Dihydroxyphenyl)ethanol, 3,4',5,7-Tetrahydroxyflavone (Kaempferol), ($\pm$)-1,2-Dithiolane-3-pentanoic acid, Luteolin, Lycopene, L-Lysine, Neochlorogenic acid, Oleic acid, trans-3,5,4'-Trihydroxystilbene (Resveratrol), 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxychromen-4-one, Rutin hydrate, Selenol-L-methionine, Thiourea, (+)- α -Tocopherol, Xanthophyll, Citric acid (CA), Gentisic acid (GA), Salicylic acid (SA), Erythorbic acid (EA), Phenol, Sodium bisulfite, Butylated hydroxy anisole, Butylated hydroxy toluene, Metabisulfite, Benzyl alcohol, Thymol, Lipoic acid (LA), Thioglycolic acid (TGA), 2,3 Dimercaptopropan-1-ol (BAL), Zinc, Selenium, Albumin, Ethanol, Mannitol, Sucrose, Melatonin, Ebselen, Pyruvic acid, Carboxy-PTIO, Trolox, Uric acid,

Edaravone, Beta carotene, NADPH, Lycopene, Lutein, Catalase, Estrogen, Estradiol, Estriol, Ubiquinol, Copper, Quercetin, Cortisone, Taurine, (2R,3R)-5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-3-yl 3,4,5-trihydroxybenzoate (EpiGallo-Catechin gallate or EGCG), (2R,3R)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3,4-dihydro-2H-chromen-3-yl] 3,4,5-trihydroxybenzoate or Epi-Catechin Gallate (ECG), (2R,3R)-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol (Epigallo-Catechin or EGC), (2R,3S)-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol (Gallo-Catechin or GC), (-)-Epigallocatechin-3-O-Gallate, 5-Aminolevulinic Acid hydrate, Ploysorbate 80, Garlic Acid, Sodium L-Ascorbate, Hyaluronic Acid, Dextran 60-90, Selenol, and LysaKare. The radiolysis stabilizer can also be a vitamin or a derivative thereof, for example, L-Ascorbic acid, β -Carotene, Provitamin A, (+)- α -Tocopherol, Erythorbic acid (EA), Trolox, and Lutein. In some embodiments, the radiolysis stabilizer is a lipid. The lipid can be a fatty acid, such as a saturated or unsaturated C₆ to C₃₀ fatty acid. In some embodiments, the fatty acid is oleic acid, Myristoleic acid, Palmitoleic acid, Sapienic acid, Elaidic acid, Vaccenic acid, or Linoleic acid, α -Linolenic acid. In another embodiment, the lipid is a steroid or derivatives thereof, for example, Estrogen, Estradiol, Estriol, or Cortisone. The radiolysis stabilizer can also be a carbohydrate or a derivative thereof, such as Mannitol, Sucrose, Dextran (e.g., Dextran 40, Dextran 70), and Cyclodextrins, (e.g., α (alpha)-cyclodextrin, β (beta)-cyclodextrin, and γ (gamma)-cyclodextrin). In some embodiments, the radiolysis stabilizer is a volume expander. The volume expander can be a polymer or a polymer mixture, such as PEG 3350, PEG 4000, Polygeline, Haemaccel, Gelofusine, and PLENVU (polyethylene glycol 3350, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride US FDA 2018 Label). In some embodiments, the volume expander is selected from Dextran, Dextran 40, Dextran 70, Cyclodextrins, α (alpha)-cyclodextrin, β (beta)-cyclodextrin, and γ (gamma)-cyclodextrin, PEG 3350, PEG 4000, Polygeline, Gelofusine, and PLENVU (polyethylene glycol 3350, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride US FDA 2018 Label). In some embodiments, radiolysis stabilizer is selected from N-Acetyl-L-cysteine, L-Ascorbic acid, N-tert-Butyl- α -phenylnitrone, 3-(3,4-Dihydroxyphenyl)-2-propenoic acid (Caffeic Acid), β -Carotene, Provitamin A, (2S,3R)-2-(3,4-Dihydroxyphenyl)-3,4-dihydro-1(2H)-benzopyran-3,5,7-triol 3-(3,4,5-trihydroxybenzoate ((-) Catechin gallate, or CG), 1,4,5-Trihydroxycyclohexanecarboxylic acid, trans-4-Hydroxycinnamic acid (p-Coumaric acid), 3,3',4',5,5',7-Hexahydroxyflavylium chloride, Thiocytic Acid (Dihydrolipoic Acid, DHLA), 4,4',5,5',6,6'-Hexahydroxydiphenic acid 2,6,2',6'-dilactone (Ellagic acid), (-)-cis-3,3',4',5,7-Pentahydroxyflavane (Epi-Catechin or EC), 2-Methoxy-4-(2-propenyl) phenol, trans-4-Hydroxy-3-methoxycinnamic acid (Ferulic acid), 7-Hydroxy-3-(4'-methoxyphenyl)-4H-benzopyran-4-one, all-trans-Fucoanthin, 3,4,5-Trihydroxybenzoic acid

(Gallic acid), (2S,3R)-2-(3,4,5-Trihydroxyphenyl)-3,4-dihydro-1(2H)-benzopyran-3,5,7-triol ((-)-Galocatechin), Glutathione, 2-(3,4-Dihydroxyphenyl)ethanol, 3,4',5,7-Tetrahydroxyflavone (Kaempferol), (±)-1,2-Dithiolane-3-pentanoic acid, Luteolin, Lycopene, L-Lysine, Neochlorogenic acid, Oleic acid, trans-3,5,4'-Trihydroxystilbene (Resveratrol), 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxychromen-4-one, Rutin hydrate, Selenol-L-methionine, Thiourea, (+)- α -Tocopherol, Xanthophyll, Alanine and its derivatives, Arginine and its derivatives, Asparagine and its derivatives, Aspartic acid and its derivatives, Cysteine and its derivatives, Glutamine and its derivatives, Glutamic acid and its derivatives, Glycine and its derivatives, Histidine and its derivatives, Isoleucine and its derivatives, Lysine and its derivatives, Methionine and its derivatives, Phenylalanine and its derivatives, Proline and its derivatives, Serine and its derivatives, Threonine and its derivatives, Tryptophan and its derivatives, Tyrosine and its derivatives, Valine and its derivatives, Citric acid (CA), Gentisic acid (GA), Salicylic acid (SA), Erythorbic acid (EA), Phenol, Sodium bisulfite, Butylated hydroxy anisole, Butylated hydroxy toluene, Glutathione, Metabisulfite, Benzyl alcohol, Thymol, Lipoic acid (LA), Thioglycolic acid (TGA), 2,3 Dimercaptopropan-1-ol (BAL), Zinc, Selenium, Albumin, Ethanol, Mannitol, Sucrose, Melatonin, Ebselen, Pyruvic acid, Carboxy-PTIO, Trolox, Uric acid, Edaravone, Beta carotene, NADPH, Lycopene, Lutein, Catalase, Estrogen, Estradiol, Estriol, Ubiquinol, Copper, Quercetin, Cortisone, 2,3-dimercaptosuccinic acid (DMSA), monisoamyl derivative (MiADMSA), Taurine, Dextran, Dextran 40, Dextran 70, PEG 3350, PEG 4000, Polygeline, Gelofusine, PLENVU (polyethylene glycol 3350, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride US FDA 2018 Label), Cyclodextrins, α (alpha)-cyclodextrin, β (beta)-cyclodextrin, and γ (gamma)-cyclodextrin, (2R,3R)-5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-3-yl 3,4,5-trihydroxybenzoate (EpiGallo-Catechin gallate or EGCg), (2R,3R)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3,4-dihydro-2H-chromen-3-yl] 3,4,5-trihydroxybenzoate or Epi-Catechin Gallate (ECG), (2R,3R)-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol (Epigallo-Catechin or EGC), and (2R,3S)-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol (Gallo-Catechin or GC).

[008] In one aspect, disclosed herein is a radiopharmaceutical composition comprising one or more stabilizing agents that further comprise a first and a second radiolysis stabilizer. In some embodiments, the first and the second radiolysis stabilizer has a molar ratio that is from 1:5 to 5:1. In one aspect, disclosed herein is a radiopharmaceutical composition comprising a radiolysis stabilizer. In some embodiments, the radiolysis stabilizer is present in the radiopharmaceutical composition at about 0.01 mM to about 5 M. In some embodiments, the stabilizing agent is

present in the radiopharmaceutical composition from about 5 mM, 10 mM, 25 mM, 50 mM, or 75mM to about 80 mM, 100 mM, 125 mM, 150 mM, 175 mM, 200 mM, 250 mM, or 500 mM. In some embodiments, the stabilizing agent is present in the radiopharmaceutical composition at about 0.1 mM to about 500 mM. In some embodiments, the stabilizing agent is present in the radiopharmaceutical composition at about 10 mM to about 500 mM. In some embodiments, the stabilizing agent is present in the radiopharmaceutical composition at about 20 mM to about 100 mM. In some embodiments, the radiolysis stabilizer is present in the radiopharmaceutical composition at about 0.0001 wt% to about 10 wt%. In some embodiments, the radiolysis stabilizer is present in the radiopharmaceutical composition at about 0.01 wt% to about 5 wt%, about 0.05 wt% to about 2 wt%, or about 0.1 wt% to about 1 wt%. In some embodiments, the radiolysis stabilizer is present in the radiopharmaceutical composition at a concentration of from about 0.1 to 50 mg/mL.

[009] In one aspect, disclosed herein is a radiopharmaceutical composition comprising one or more stabilizing agents that comprise a free metal chelator, which is not attached to the targeting ligand. In some embodiments, the free metal chelator is selected from Ethylenediaminetetraacetic acid (EDTA), Diethylenetriaminepentaacetic acid (DTPA), 2-S-(4-Isothiocyanatobenzyl)-1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA), Triethylenetetramine (TETA), 1, 4, 7, 10, 13-pentaazacyclopentadecane-N, N', N'', N''', N''''-pentaacetic acid (PEPA), 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetrapropionic acid (TETPA), triethylenetetraminepentaacetic acid, 2,2',2''-(10-(2,6-dioxotetrahydro-2H-pyran-3-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (DOTA-GA), 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic acid (DOTP), Deferoxamine (DFO), N, N-bis(2-hydroxybenzyl)ethylenediamine-N,N-diacetic acid (HBED), 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic acid) (DOTP), 6,6'-((1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))dipicolinic acid (Macropa), Meso-2,3-dimercaptosuccinic acid (DMSA), Dimercaptopropane sulfonate (DMPS), Dihydrolipoic acid (DHLA), Lipoic acid (LA), Thioglycolic acid (TGA), and 2,3 Dimercaptopropan-1-ol (BAL). In some embodiments, the free metal chelator is EDTA, DTPA, or Macropa. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at about 0.001 wt% to about 10 wt%. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at about 0.01 wt% to about 5 wt%, about 0.05 wt% to about 2 wt%, or about 0.1 wt% to about 1 wt%. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at a concentration of from 0.01 to 50 mg/mL. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at about 10 mM to about 500 mM.

[010] In one aspect, disclosed herein is a radiopharmaceutical composition comprising one or

more stabilizing agents that comprise one or more pH stabilizers. In one aspect, disclosed herein is a radiopharmaceutical composition comprising a pH stabilizer. In some embodiments, the pH stabilizer is the same as the radiolysis stabilizer. The pH stabilizers can function as a pH buffer. In some embodiments, the one or more pH stabilizers comprise an organic acid, such as an acetic acid, fumaric acid, ascorbic acid, propionic acid, benzene sulfonic acid, carbonic acid, citrate acid, aspartic acid, maleic acid, methane sulfonic acid, or tartaric acid. In some embodiments, the one or more pH stabilizers comprise an inorganic acid, for example, hydrobromic acid, hydrochloric acid, phosphoric acid, boric acid, or sulfuric acid. In some embodiments, the one or more pH stabilizers can comprise a base, such as tromethamine (Tris), ammonium hydroxide, diethanolamine, or sodium hydroxide. In some embodiments, the one or more pH stabilizers can also comprise an amino acid or a salt thereof. In some embodiments, the amino acid is glycine, lysine, arginine, histidine, or a salt thereof. In another embodiment, the one or more pH stabilizers comprise an alkaline salt, for example, sodium acetate, sodium ascorbate, sodium benzoate, sodium bicarbonate, sodium carbonate, tribasic sodium phosphate acid, dibasic sodium phosphate acid, monobasic sodium phosphate acid, sodium tartrate, sodium lactate, sodium succinate, or disodium succinate. In some embodiments, the one or more pH stabilizers can comprise an acid salt, such as ammonium sulfate. In some embodiments, the one or more pH stabilizers comprise Sodium acetate, Sodium ascorbate, Ascorbic acid, Acetic 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, 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, tromethamine (tris), or a combination thereof. In some embodiments, the one or more pH stabilizers are present in the radiopharmaceutical composition at about 0.001 wt% to about 10 wt%. In some embodiments, one or more pH stabilizers are present in the radiopharmaceutical composition at about 0.01 wt% to about 5 wt%, about 0.05 wt% to about 2 wt%, or about 0.1 wt% to about 1 wt%. In some embodiments, the one or more pH stabilizers are present in the radiopharmaceutical composition at a concentration of from 0.1 to 5 mg/mL. In some embodiments, the one or more pH stabilizers are present in the radiopharmaceutical composition at about 10 mM to about 500 mM. The one or more pH stabilizers can be configured to maintain a pH of the radiopharmaceutical composition at about 4 to about 8. The one or more pH stabilizers can be configured to maintain a pH of the radiopharmaceutical composition at about 5 to about 7. In some embodiments, the pH of the radiopharmaceutical composition is within a range of about 4 to about 8. In some embodiments,

the pH of the radiopharmaceutical composition is about 5.5 to about 6.0. The radiopharmaceutical composition can comprise one or more radiolysis stabilizers, one or more free metal chelators, and/or one or more pH stabilizers.

[011] In one aspect, disclosed herein is a radiopharmaceutical composition comprising an aqueous vehicle. The aqueous vehicle can comprise water (e.g., water for injection), saline solution, dextrose in water, dextrose in saline solution, Ringer's solution, or lactated Ringer's solution. The radiopharmaceutical composition can be isotonic. The radiopharmaceutical composition can be a solution or suspension. In some embodiments, the radiopharmaceutical composition is formulated for IV infusion or bolus injection. In some embodiments, the radiopharmaceutical composition further comprises one or more excipients selected from: a tonicity adjusting agent, a preservative, an antimicrobial agent, a solubilizing agent, a suspending agent, and a surfactant.

[012] In one aspect, disclosed herein is a radiopharmaceutical composition comprising a conjugate that further comprises a targeting ligand that covalently links to a metal chelator through a linker. In some embodiments, the targeting ligand is a binding peptide, and the linker is attached to the binding peptide via the N terminus of the peptide. In some embodiments, the targeting ligand is a binding peptide, and the linker is attached to the binding peptide via the C terminus of the peptide. In some embodiments, the targeting ligand is a binding peptide, and the linker is attached to the binding peptide via a non-terminal amino acid of the peptide. The linker can comprise one or more groups selected from: substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[013] In one aspect, disclosed herein is a radiopharmaceutical composition comprising a conjugate that further comprises a radionuclide. The radionuclide can be an alpha particle-emitting radionuclide, such as actinium-225, astatine-211, thorium-227, or radium-223. In some embodiments, the alpha particle-emitting radionuclide is actinium-225. In some embodiments, the actinium-225 is present in the radiopharmaceutical composition that it provides a volumetric radioactivity of about 0.5 to 20 MBq/mL. In some embodiments, the conjugate is ²²⁵Ac-DOTATATE. In another embodiment, the conjugate is ²²⁵Ac-DOTATOC. In some embodiments, the radiopharmaceutical composition retains at least 90 mol% of the initial conjugate after 168 hours at room temperature. In some embodiments, the composition retains at least 95 mol% of the initial conjugate after 168 hours at room temperature. In some embodiments, the composition retains at least 98 mol% of the initial conjugate after 168 hours at room temperature. In some embodiments, the composition retains at least 85 mol%, at least 90 mol%, at least 92 mol%, at least 95 mol%, at least 98 mol% or at least 99 mol% of the initial conjugate after 120 hours at

room temperature. In some embodiments, the composition retains 95 mol% or more of the initial conjugate after 48 hours, 72 hours, 96 hours, 120 hours, 148 hours, 168 hours, 192 hours, or 216 hours at room temperature. In some embodiments, the radionuclide is actinium-225, and wherein the composition contains no more than about 5% free actinium after 168 hours at room temperature, compared to the total amount of the initial chelated actinium content in the composition. In some embodiments, the radionuclide is actinium-225, and wherein the composition contains no more than about 2% or about 1% free actinium after 168 hours at room temperature, compared to the total amount of the initial chelated actinium content in the composition. In some embodiments, the radionuclide is actinium-225, and wherein the composition contains no more than a total of 5 mol% of free daughter isotopes of actinium-225 after 168 hours at room temperature, compared to the total amount of the initial chelated actinium content in the composition. In some embodiments, the radionuclide is actinium-225, and wherein the composition contains no more than a total of 1 mol% of un-chelated (free) daughter isotopes of actinium-225 after 168 hours at room temperature, compared to the total amount of the initial chelated actinium content in the composition. In some embodiments, the purity or the molar percentage of the initial conjugate is determined by radio thin layer chromatography (radio-TLC). In some embodiments, the purity or the molar percentage of the initial conjugate is determined by instant thin layer chromatography (iTLC).

[014] In one aspect, disclosed herein is a radiopharmaceutical composition, comprising: (a) the conjugate, wherein the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 0.1 to about 100 mCi/L (e.g., about 10 to about 50 mCi/L, about 0.5 to about 100 mCi/L, 1 to about 50 mCi/L); (b) a radiolysis stabilizer, wherein the radiolysis stabilizer is present in the radiopharmaceutical composition at a concentration of about 50 to about 200 mM (e.g., about 80 to about 120 mM); (c) optionally a pH stabilizer, wherein the pH stabilizer is present in the radiopharmaceutical composition at concentration of about 0.1 wt% to about 10wt%; (d) a free metal chelator, wherein the free metal chelator is present in the radiopharmaceutical composition at concentration of about 0.01 mg/mL to about 5 mg/mL (e.g., about 0.01 mg/mL to about 1 mg/mL); and (e) an aqueous vehicle. In one aspect, disclosed herein is a radiopharmaceutical composition, comprising: (a) the conjugate, wherein the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 1 to 50 mCi/L (e.g., about 10 to 50 mCi/L) ; (b) a radiolysis stabilizer, wherein the radiolysis is ascorbic acid or a salt thereof (e.g., sodium L-ascorbate) and is present in the radiopharmaceutical composition at a concentration of about 50 to about 200 mM (e.g., about 80 to about 120 mM); (c) a free metal chelator, wherein the free metal chelator is selected from EDTA, macropa, TETA, PEPA, TETPA, DFO, DOPT, DHLA, TGA, LA, and DTPA, or a combination thereof, and

wherein the free metal chelator is present in the radiopharmaceutical composition at a concentration of about 0.01 mg/mL to about 1 mg/mL; and (d) an aqueous vehicle, wherein the aqueous vehicle is saline solution. In some embodiments, the radiopharmaceutical composition further comprises a pH stabilizer. In some embodiments, the radiopharmaceutical composition further comprises a second radiolysis stabilizer. In some embodiments, the second radiolysis stabilizer (e.g., Dextran 40) is present in the radiopharmaceutical composition at a concentration of about 1 wt% to about 10wt%. In some embodiments, the second radiolysis stabilizer is present in the radiopharmaceutical composition at a concentration of about 0.05 wt% to about 5 wt%. In one aspect, disclosed herein is a radiopharmaceutical composition, comprising: (a) the conjugate, wherein the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 1 to 50 mCi/L (e.g., about 10 to 50 mCi/L); (b) a radiolysis stabilizer; (c) optionally, a pH stabilizer, wherein the pH stabilizer is configured to maintain a pH of the radiopharmaceutical composition at about 4 to 8; (d) a free metal chelator, wherein the free metal chelator is configured to maintain a level of free radionuclide in the radiopharmaceutical composition below about 0.05 mCi/L; and (e) an aqueous vehicle. In some embodiments, the radiolysis stabilizer (such as ascorbic acid or sodium ascorbate) can function as a pH stabilizer. In some embodiments, the radiolysis stabilizer and the pH stabilizer is the same compound. In one aspect, disclosed herein is a radiopharmaceutical composition, comprising: (a) the conjugate, wherein the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 0.5 to 50 mCi/L; (b) a radiolysis stabilizer; and (c) optionally, a pH stabilizer, wherein the pH stabilizer is configured to maintain a pH of the radiopharmaceutical composition at about 4 to 8; (d) a free metal chelator, wherein the free metal chelator is configured to maintain a level of free radionuclide in the radiopharmaceutical composition below about 0.05 mCi/L; and (e) an aqueous vehicle. In some embodiments, the radiolysis stabilizer (such as ascorbic acid or sodium ascorbate) can function as a pH stabilizer. In some embodiments, the radiolysis stabilizer and the pH stabilizer is the same compound. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 2 to 50 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 5 to 50 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 1 to 100 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 to 50 mCi/L.

[015] In one aspect, the present disclosure relates to a method of making a radiopharmaceutical composition described herein. In some embodiments, the method of making the radiopharmaceutical composition comprises combining a radionuclide (such as ²²⁵Ac) with an -

un-labeled conjugate (e.g., DOTATATE or DOTATOC) in the presence of one or more stabilizer agents, wherein the un-labeled conjugate comprises a targeting ligand and a metal chelator covalently attached to the targeting ligand, thereby producing a mixture comprising a labeled conjugate (e.g., ^{225}Ac -DOTATATE or ^{225}Ac -DOTATOC), and optionally combining one or more stabilizing agents to the mixture. In some embodiments, the method of making the radiopharmaceutical composition comprises combining a radionuclide (such as ^{225}Ac) with an un-labeled conjugate (e.g., DOTATATE or DOTATOC), wherein the un-labeled conjugate comprises a targeting ligand and a metal chelator covalently attached to the targeting ligand, thereby producing a labeled conjugate, and combining the one or more stabilizing agents with the labeled conjugate.

[016] In one aspect, the present disclosure relates to a method of treating a disease in a subject in need thereof comprising administering to the subject the radiopharmaceutical composition described herein. The disease can be a cancer. In some embodiments, the cancer is an SSR-associated cancer, such as an SSTR2-associated cancer. The cancer can be a neuroendocrine cancer, a lymphatic cancer, a pancreatic cancer, a pituitary cancer, a breast cancer, a stomach cancer, a lung cancer, medulloblastoma, or neuroblastoma. In some embodiments, the cancer is a neuroendocrine cancer, which can optionally be recurrent. In some embodiments, the neuroendocrine cancer is refractory to a radiotherapy that comprises beta-particle emitting radionuclide. In some embodiments, the subject has received a radiotherapy that comprises beta-particle emitting radionuclide prior to the administering of the radiopharmaceutical composition described herein. The neuroendocrine cancer can also be a neuroendocrine lung cancer or a neuroendocrine pancreatic cancer. In some embodiments, the neuroendocrine cancer is a Carcinoid tumor in the lungs, gastrointestinal tract or thymus, Pancreatic neuroendocrine tumor (e.g., Gastrinoma, Insulinoma, Glucagonoma, VIPoma, gastroenteropancreatic neuroendocrine tumor) Medullary thyroid carcinoma, Merkel cell carcinoma, Pheochromocytoma of the adrenal gland, Adrenal cancer, Small cell carcinoma (such as in the lungs), or Large cell carcinoid tumor (such as in the lungs). In some embodiments, the lung cancer is small-cell lung cancer. In some embodiments, the lung cancer is extensive stage small cell lung cancer. In some embodiments, the cancer is untreated. In some embodiments, the cancer is recurrent or refractory. In some embodiments, the small-cell lung cancer is untreated. In some embodiments, the small-cell lung cancer is recurrent or refractory. In some embodiments, the radiopharmaceutical composition is administered to the subject in an amount equivalent to about 1kBq/kg to about 0.2GBq/kg body weight per dose. In some embodiments, the radiopharmaceutical composition is administered to the subject in an amount equivalent to about 5kBq/kg to about 50,000kBq/kg body weight per dose. In some embodiments, the radiopharmaceutical composition is administered to the subject

in an amount equivalent to about 20k Bq/kg to about 5,000kBq/kg body weight per dose. In some embodiments, the radiopharmaceutical composition is administered to the subject in an amount equivalent to about 50k Bq/kg to about 500 kBq/kg body weight per dose. In some embodiments, the radiopharmaceutical composition is administered to the subject in an amount equivalent to about 50k Bq/kg to about 200 kBq/kg body weight per dose. In some embodiments, the radiopharmaceutical composition is administered to the subject in an amount equivalent to about 60 kBq/kg to about 150 kBq/kg body weight per dose. In some embodiments, the radiopharmaceutical composition is administered to deliver a radioactivity dose of about 1 to 1,000 μ Ci. In some embodiments, the radiopharmaceutical composition is administered to deliver a radioactivity dose of about 10 to 500 μ Ci. In some embodiments, the radiopharmaceutical composition is administered to deliver a radioactivity dose of about 100 to 500 μ Ci. In some embodiments, the radiopharmaceutical composition is administered to deliver a radioactivity dose of about 100 to 300 μ Ci. In some embodiments, the radiopharmaceutical composition is administered to deliver a radioactivity dose of about 150 to 300 μ Ci. In some embodiments, the radiopharmaceutical composition is administered to deliver a radioactivity dose of about 175 to 275 μ Ci. In some embodiments, the radiopharmaceutical composition is administered at an 8-week interval. In some embodiments, the radiopharmaceutical composition is administered to achieve a cumulative dose in the subject of about 10,000 kBq to about 100,000 kBq. In some embodiments, the radiopharmaceutical composition is administered to achieve a cumulative dose in the subject of about 40,000 kBq to about 70,000 kBq.

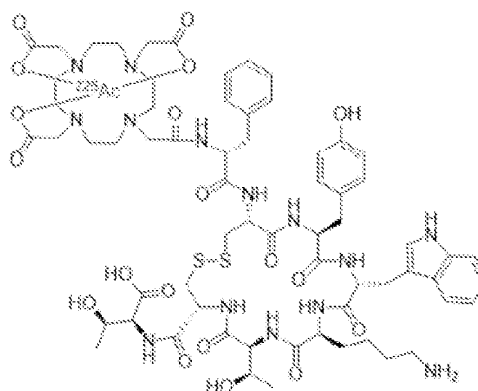
[017] In one aspect, provided herein is a dilution solution comprising one or more stabilizing agents and an aqueous vehicle.

[018] In one aspect, provided herein is a liquid radiopharmaceutical composition comprising: (a) ^{225}Ac -DOTA-TATE, wherein the ^{225}Ac -DOTA-TATE is present in the radiopharmaceutical composition at a concentration equivalent to about 10 mCi/L to about 30 mCi/L; (b) sodium L-ascorbate, wherein the sodium L-ascorbate is present in the radiopharmaceutical composition at a concentration of about 80 mM to about 110 mM; (c) diethylenetriamine pentaacetate (DTPA), wherein the DTPA is present in the radiopharmaceutical composition at a concentration of about 0.04 mg/mL to about 0.06 mg/mL; and (d) an aqueous vehicle, wherein the aqueous vehicle is sodium chloride saline solution at a concentration of about 0.9% w/w; wherein the radiopharmaceutical composition is a solution, and wherein the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content as ^{225}Ac -DOTA-TATE after 120 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC). In one aspect, provided herein is a liquid radiopharmaceutical composition consisting essentially of: (a) ^{225}Ac -DOTA-TATE, wherein the ^{225}Ac -DOTA-TATE is present in the radiopharmaceutical

composition at a concentration equivalent to about 10 mCi/L to about 30 mCi/L; (b) sodium L-ascorbate, wherein the sodium L-ascorbate is present in the radiopharmaceutical composition at a concentration of about 80 mM to about 110 mM; (c) diethylenetriamine pentaacetate (DTPA), wherein the DTPA is present in the radiopharmaceutical composition at a concentration of about 0.04 mg/mL to about 0.06 mg/mL; and (d) an aqueous vehicle, wherein the aqueous vehicle is sodium chloride saline solution at a concentration of about 0.9% w/w; wherein the radiopharmaceutical composition is a solution, and wherein the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content as ^{225}Ac -DOTA-TATE after 120 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC). In one aspect, provided herein is a liquid radiopharmaceutical composition consisting of: (a) ^{225}Ac -DOTA-TATE, wherein the ^{225}Ac -DOTA-TATE is present in the radiopharmaceutical composition at a concentration equivalent to about 10 mCi/L to about 30 mCi/L; (b) sodium L-ascorbate, wherein the sodium L-ascorbate is present in the radiopharmaceutical composition at a concentration of about 90 mM to about 110 mM; (c) diethylenetriamine pentaacetate (DTPA), wherein the DTPA is present in the radiopharmaceutical composition at a concentration of about 0.04 mg/mL to about 0.06 mg/mL; and (d) an aqueous vehicle, wherein the aqueous vehicle is sodium chloride saline solution at a concentration of about 0.9% w/w; wherein the radiopharmaceutical composition is a solution, and wherein the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content as ^{225}Ac -DOTA-TATE after 120 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC). In some embodiments, the ^{225}Ac -DOTA-TATE is present in the radiopharmaceutical composition at a concentration equivalent to about 10 mCi/L to about 25 mCi/L. In some embodiments, the ^{225}Ac -DOTA-TATE is present in the radiopharmaceutical composition at a concentration equivalent to about 12 mCi/L to 23 mCi/L. In some embodiments, the ^{225}Ac -DOTA-TATE is present in the radiopharmaceutical composition at a concentration equivalent to about 40 μg to about 120 μg of the DOTA-TATE. In some embodiments, the sodium ascorbate is present in the radiopharmaceutical composition at a concentration of about 100mM. In some embodiments, the DTPA is present in the radiopharmaceutical composition at a concentration of about 0.05mg/mL. In some embodiments, the composition retains at least 90 % of the ^{225}Ac content as ^{225}Ac -DOTA-TATE after 168 hours at about 20°C to about 25°C. In some embodiments, the composition retains at least 90 % of the ^{225}Ac content as ^{225}Ac -DOTA-TATE after 192 hours at about 20°C to about 25°C. In some embodiments, the radiopharmaceutical composition is formulated as a unit dose form that contains about 12mL of the solution, and wherein the liquid radiopharmaceutical composition consists of: (a) ^{225}Ac -DOTA-TATE present in the radiopharmaceutical composition in an amount of 146-275 μCi in the about 12 mL solution; (b) sodium L-ascorbate present in the radiopharmaceutical

composition at a concentration of about 18.5 mg/mL; (c) DTPA, present in the radiopharmaceutical composition at a concentration of about 0.05 mg/mL; and (d) sodium chloride saline solution at a concentration of about 0.9% w/w. In some embodiments, the liquid radiopharmaceutical composition has a pH of about 5.5 to about 7.0. In some embodiments, the radiopharmaceutical composition is formulated for IV infusion.

[019] In one aspect, provided herein is a liquid radiopharmaceutical composition wherein the



²²⁵Ac-DOTA-TATE has a structure illustrated as:

[020] In one aspect, provided herein is a method of treating a somatostatin receptor-positive (SSTR+) neuroendocrine tumor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a liquid radiopharmaceutical composition, wherein the liquid radiopharmaceutical composition comprises: (a) ²²⁵Ac-DOTA-TATE, wherein the ²²⁵Ac-DOTA-TATE is present in the radiopharmaceutical composition at a concentration equivalent to about 10 mCi/L to about 30 mCi/L; (b) sodium L-ascorbate, wherein the sodium L-ascorbate is present in the radiopharmaceutical composition at a concentration of about 90 mM to about 110 mM; (c) diethylenetriamine pentaacetate (DTPA), wherein the DTPA is present in the radiopharmaceutical composition at a concentration of about 0.04 mg/mL to about 0.06 mg/mL; and (d) an aqueous vehicle, wherein the aqueous vehicle is sodium chloride saline solution at a concentration of about 0.9% w/w; wherein the radiopharmaceutical composition is a solution, and wherein the radiopharmaceutical composition retains at least 90 % of the ²²⁵Ac content as ²²⁵Ac-DOTA-TATE after 120 hours at about 20° to about 25°C as determined by radio thin-layer chromatography (radio-TLC).

[021] In one aspect, provided herein is a method of treating a somatostatin receptor-positive (SSTR+) neuroendocrine tumor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a liquid radiopharmaceutical composition, wherein the liquid radiopharmaceutical composition consists essentially of: (a) ²²⁵Ac-DOTA-TATE, wherein the ²²⁵Ac-DOTA-TATE is present in the radiopharmaceutical composition at a concentration equivalent to about 10 mCi/L to about 30 mCi/L; (b) sodium L-ascorbate, wherein

the sodium L-ascorbate is present in the radiopharmaceutical composition at a concentration of about 90 mM to about 110 mM; (c) diethylenetriamine pentaacetate (DTPA), wherein the DTPA is present in the radiopharmaceutical composition at a concentration of about 0.04 mg/mL to about 0.06 mg/mL; and (d) an aqueous vehicle, wherein the aqueous vehicle is sodium chloride saline solution at a concentration of about 0.9% w/w; wherein the radiopharmaceutical composition is a solution, and wherein the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content as ^{225}Ac -DOTA-TATE after 120 hours at about 20° to about 25°C as determined by radio thin-layer chromatography (radio-TLC).

[022] In one aspect, provided herein is a method of treating a somatostatin receptor-positive (SSTR+) neuroendocrine tumor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a liquid radiopharmaceutical composition, wherein the liquid radiopharmaceutical composition consists of: (a) ^{225}Ac -DOTA-TATE, wherein the ^{225}Ac -DOTA-TATE is present in the radiopharmaceutical composition at a concentration equivalent to about 10 mCi/L to about 30 mCi/L; (b) sodium L-ascorbate, wherein the sodium L-ascorbate is present in the radiopharmaceutical composition at a concentration of about 90 mM to about 110 mM; (c) diethylenetriamine pentaacetate (DTPA), wherein the DTPA is present in the radiopharmaceutical composition at a concentration of about 0.04 mg/mL to about 0.06 mg/mL; and (d) an aqueous vehicle, wherein the aqueous vehicle is sodium chloride saline solution at a concentration of about 0.9% w/w; wherein the radiopharmaceutical composition is a solution, and wherein the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content as ^{225}Ac -DOTA-TATE after 120 hours at about 20° to about 25°C as determined by radio thin-layer chromatography (radio-TLC). In some embodiments, the neuroendocrine tumor is gastroenteropancreatic neuroendocrine tumor (GEP-NET). In some embodiments, the subject received ^{177}Lu -DOTA-TATE or ^{177}Lu -DOTA-TOC treatment prior to the administering of the liquid radiopharmaceutical composition. In some embodiments, prior to the administering of the liquid radiopharmaceutical composition, the subject received ^{177}Lu -DOTA-TATE or ^{177}Lu -DOTA-TOC treatment and the tumor has progressed. In some embodiments, the radiopharmaceutical composition is administered to the subject in an amount equivalent to about 60 kBq/kg body weight to 120 kBq/kg body weight per dose. In some embodiments, the radiopharmaceutical composition is administered at an 8-week interval. In some embodiments, the ^{225}Ac -DOTA-TATE is present in the radiopharmaceutical composition at a concentration equivalent to about 10 mCi/L to about 25 mCi/L.

[023] In one aspect, provided herein is a method of treating a somatostatin receptor-positive (SSTR+) neuroendocrine tumor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a liquid radiopharmaceutical composition, wherein

the liquid radiopharmaceutical composition consists of: (a) ^{25}Ac -DOTA-TATE present in the radiopharmaceutical composition at a concentration equivalent to 10 mCi/L to 25 mCi/L; (b) sodium L-ascorbate present in the radiopharmaceutical composition at a concentration of about 100mM; (c) DTPA, present in the radiopharmaceutical composition at a concentration of about 0.05 mg/mL; and (d) sodium chloride saline solution at a concentration of about 0.9% w/w.

[024] In one aspect, provided herein is a method of treating a somatostatin receptor-positive (SSTR+) neuroendocrine tumor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a liquid radiopharmaceutical composition, wherein the liquid radiopharmaceutical composition is formulated as a unit dose form that has about 12mL of the solution, and wherein the liquid radiopharmaceutical composition consists of: (a) ^{225}Ac -DOTA-TATE present in the radiopharmaceutical composition in an amount of 146 – 275 μCi in about 12 mL solution; (b) sodium L-ascorbate present in the radiopharmaceutical composition at a concentration of about 18.5 mg/mL; (c) DTPA present in the radiopharmaceutical composition at a concentration of about 0.05 mg/mL; and (d) sodium chloride saline solution at a concentration of about 0.9% w/w.

INCORPORATION BY REFERENCE

[025] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference for the specific purposes identified herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[026] The novel features of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawing (also “figure” and “FIG.” herein), of which:

[027] FIG. 1A depicts the structures of exemplary radiolysis stabilizers catechins and their derivatives; FIG. 1B illustrates the structures of exemplary stabilizing agents cyclodextrin; FIG. 1C illustrates the structures of exemplary stabilizing agents (antioxidants); FIG. 1D illustrates the structures of exemplary stabilizing agents (amino acids); and FIG. 1E illustrates the structures of exemplary stabilizing agents.

[028] FIG. 2A illustrates the structures of exemplary small molecule targeting ligands; FIG. 2B illustrates the structures of exemplary binding peptide.

[029] FIG. 3- FIG. 17 depict the structures of representative metal chelators.

[030] FIG. 18A and FIG. 18B illustrate the abbreviations and modification of amino acids.

[031] FIG. 19 depicts a clinical treatment dosing schedule using ^{225}Ac -DOTA-TATE. Patients receive a de-escalating dose scheme and will receive up to 4 cycles of ^{225}Ac -DOTA-TATE every 8 weeks.

[032] FIG. 20A illustrates stained tissue samples having an H-score of 281, 160 or 90; FIG. 20B illustrates stained tissue samples of normal lung or pancreatic NET.

[033] FIG. 21 depicts a clinical treatment dosing schedule ^{225}Ac -DOTA-TATE. Patients receive an escalating dose structure and will receive 4-6 cycles of ^{225}Ac -DOTA-TATE once every 6 weeks during standard of care therapy (PD-L1i + CE) and once every 4 weeks during PD-L1 maintenance phase for a maximum of 6 infusions. PD-L1i represents a PD-L1 inhibitor; C represents carboplatin or cisplatin; E represents etoposide. ^{225}Ac -DOTA-TATE is administered earlier than or on the same day with PD-L1i, C, and E.

[034] FIG. 22 depicts a clinical trial Simon 2-stage cohort expansion study. The 1L-ES-SCLC cohort will receive ^{225}Ac -DOTA-TATE in combination with standard of care therapy (PD-L1i + CE). The 2L-ES-SCLC cohort will receive ^{225}Ac -DOTA-TATE in combination with CE. 1L-ES-SCLC represents first line extensive stage small cell lung cancer; 2L-ES-SCLC represents second line extensive stage small cell lung cancer; PD-L1i represents a PD-L1 inhibitor; C represents carboplatin or cisplatin; E represents etoposide; DoR represents duration of response; CR represents complete response; PR represents partial response.

[035] FIG. 23A and FIG. 23B illustrate the mean tumor volume and mean body weight respectively in a mouse study with [^{225}Ac]Ac-DOTA-TATE and [^{225}Ac]Ac-DOTA-JR-11.

DETAILED DESCRIPTION

[036] The following description and examples illustrate embodiments of the present disclosure in detail. It is to be understood that this present disclosure is not limited to the particular embodiments described herein and as such can vary. Those of skill in the art will recognize that there are numerous variations and modifications of this present disclosure, which are encompassed within its scope.

[037] Although various features of the present disclosure may be described in the context of a single embodiment, the features may also be provided separately or in any suitable combination. Conversely, although the present disclosure may be described herein in the context of separate embodiments for clarity, the present disclosure may also be implemented in a single embodiment.

[038] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[039] All terms are intended to be understood as they would be understood by a person skilled in the art. Unless defined otherwise, all technical and scientific terms used herein have the same

meaning as commonly understood by one of ordinary skill in the art to which the disclosure pertains.

[040] The following definitions supplement those in the art and are directed to the current application and are not to be imputed to any related or unrelated case, e.g., to any commonly owned patent or application. Although any methods and materials similar or equivalent to those described herein can be used in the practice for testing of the present disclosure, the preferred materials and methods are described herein. Accordingly, the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

I. Definitions

[041] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[042] As used herein and in the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “an agent” includes a plurality of such agents, reference to “a stabilizer” includes a plurality of such stabilizers, and reference to “the cell” includes reference to one or more cells (or to a plurality of cells) and equivalents thereof known to those skilled in the art, and so forth. When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included.

[043] The term “about” or “approximately” can mean within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, *i.e.*, the limitations of the measurement system. For example, “about” can mean within 1 or more than 1 standard deviation, per the practice in the art. Alternatively, “about” can mean a range of up to 20%, up to 15%, up to 10%, up to 5%, or up to 1% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, within 5-fold, or within 2-fold, of a value.

[044] The term “comprising” (and related terms such as “comprise” or “comprises” or “having” or “including”) is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, “consist of” or “consist essentially of” the described features.

[045] “Radiolysis” refers to the decay of radionuclides accompanied by emission of energy in the form of alpha, beta and/or gamma radiations. The energy that goes into the drug-containing formulation can break chemical bonds and can generate reactive chemical species from solvent molecules, which may further decompose the radiopharmaceutical drug directly and/or indirectly.

[046] “Amino” refers to the -NH_2 radical.

[047] "Nitro" refers to the -NO₂ radical.

[048] "Oxo" refers to the =O radical.

[049] "Imino" refers to the =N-H radical.

[050] "Hydroxy" or "hydroxyl" refers to the -OH radical.

[051] "Alkyl" refers to an optionally substituted straight-chain, or optionally substituted branched-chain saturated hydrocarbon monoradical. An alkyl group can have from one to about twenty carbon atoms, from one to about ten carbon atoms, or from one to six carbon atoms. Examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, tert-amyl, and hexyl, and longer alkyl groups, such as heptyl, octyl, and the like. Whenever it appears herein, a numerical range such as "C₁-C₆ alkyl" means that the alkyl group consists of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated. In some embodiments, the alkyl is a C₁-C₁₀ alkyl, a C₁-C₉ alkyl, a C₁-C₈ alkyl, a C₁-C₇ alkyl, a C₁-C₆ alkyl, a C₁-C₅ alkyl, a C₁-C₄ alkyl, a C₁-C₃ alkyl, a C₁-C₂ alkyl, or a C₁ alkyl. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkyl is optionally substituted with oxo, halogen, -CN, -CF₃, -OH, -OMe, -NH₂, -NO₂, or -C≡CH. In some embodiments, the alkyl is optionally substituted with oxo, halogen, -CN, -CF₃, -OH, or -OMe. In some embodiments, the alkyl is optionally substituted with halogen.

[052] The term "aryl" refers to a radical comprising at least one aromatic ring wherein each of the atoms forming the ring is a carbon atom. Aryl groups can be optionally substituted. Examples of aryl groups include, but are not limited to phenyl, and naphthyl. In some embodiments, the aryl is phenyl. Depending on the structure, an aryl group can be a monoradical or a diradical (i.e., an arylene group). Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals that are optionally substituted. In some embodiments, an aryl group comprises a partially reduced cycloalkyl group defined herein (e.g., 1,2-dihydronaphthalene). In some embodiments, an aryl group comprises a fully reduced cycloalkyl group defined herein (e.g., 1,2,3,4-tetrahydronaphthalene). When aryl comprises a cycloalkyl group, the aryl is bonded to the rest of the molecule through an aromatic ring carbon atom. An aryl radical can be a monocyclic or polycyclic (e.g., bicyclic, tricyclic, or

tetracyclic) ring system, which may include fused, spiro or bridged ring systems. Unless stated otherwise specifically in the specification, an aryl may be optionally substituted, for example, with halogen, amino, alkylamino, aminoalkyl, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, $-S(O)_2NH-C_1-C_6$ alkyl, and the like. In some embodiments, an aryl is optionally substituted with halogen, methyl, ethyl, $-CN$, $-CF_3$, $-OH$, $-OMe$, $-NH_2$, $-NO_2$, $-S(O)_2NH_2$, $-S(O)_2NHCH_3$, $-S(O)_2NHCH_2CH_3$, $-S(O)_2NHCH_2(CH_3)_2$, $-S(O)_2N(CH_3)_2$, or $-S(O)_2NHC(CH_3)_3$. In some embodiments, an aryl is optionally substituted with halogen, methyl, ethyl, $-CN$, $-CF_3$, $-OH$, or $-OMe$. In some embodiments, the aryl is optionally substituted with halogen. In some embodiments, the aryl is substituted with alkyl, alkenyl, alkynyl, haloalkyl, or heteroalkyl, wherein each alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl is independently unsubstituted, or substituted with halogen, methyl, ethyl, $-CN$, $-CF_3$, $-OH$, $-OMe$, $-NH_2$, or $-NO_2$.

[053] The term “cycloalkyl” refers to a monocyclic or polycyclic non-aromatic radical, wherein each of the atoms forming the ring (i.e., skeletal atoms) is a carbon atom. In some embodiments, cycloalkyls are saturated or partially unsaturated. In some embodiments, cycloalkyls are spirocyclic or bridged compounds. In some embodiments, cycloalkyls are fused with an aromatic ring (in which case the cycloalkyl is bonded through a non-aromatic ring carbon atom). Cycloalkyl groups include groups having from 3 to 10 ring atoms. Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to ten carbon atoms, from three to eight carbon atoms, from three to six carbon atoms, or from three to five carbon atoms. Monocyclic cycloalkyl radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. In some embodiments, the monocyclic cycloalkyl is cyclopentyl. In some embodiments, the monocyclic cycloalkyl is cyclopentenyl or cyclohexenyl. In some embodiments, the monocyclic cycloalkyl is cyclopentenyl. Polycyclic radicals include, for example, adamantyl, 1,2-dihydronaphthalenyl, 1,4-dihydronaphthalenyl, tetraaryl, decalyl, 3,4-dihydronaphthalenyl-1(2H)-one, spiro[2.2]pentyl, norbornyl and bicycle[1.1.1]pentyl. Unless otherwise stated specifically in the specification, a cycloalkyl group may be optionally substituted. Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to fifteen carbon atoms (C_3-C_{15} cycloalkyl), from three to ten carbon atoms (C_3-C_{10} cycloalkyl), from three to eight carbon atoms (C_3-C_8 cycloalkyl), from three to six carbon atoms (C_3-C_6 cycloalkyl), from three to five carbon atoms (C_3-C_5 cycloalkyl), or three to four carbon atoms (C_3-C_4 cycloalkyl). A cycloalkyl can comprise a fused, spiro or bridged ring system. In some embodiments, the cycloalkyl comprises a fused ring system. In some embodiments, the cycloalkyl comprises a spiro ring system. In some embodiments, the cycloalkyl comprises a bridged ring system. In some embodiments, the cycloalkyl is a 3- to 6-membered cycloalkyl. In some embodiments, the

cycloalkyl is a 5- to 6-membered cycloalkyl. Monocyclic cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls or carbocycles include, for example, adamantyl, norbornyl, decalinyl, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, cis-decalin, trans-decalin, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, and bicyclo[3.3.2]decane, and 7,7-dimethyl-bicyclo[2.2.1]heptanyl. Partially saturated cycloalkyls include, for example, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Unless stated otherwise specifically in the specification, a cycloalkyl is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the cycloalkyl is optionally substituted with halogen.

[054] Heteroalkyl” refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, e.g., oxygen, nitrogen (e.g., -NH-, -N(alkyl)-), sulfur, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C₁-C₆ heteroalkyl wherein the heteroalkyl is comprised of 1 to 6 carbon atoms and one or more atoms other than carbon, e.g., oxygen, nitrogen (e.g., -NH-, -N(alkyl)-), sulfur, or combinations thereof wherein the heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. Examples of such heteroalkyl are, for example, -CH₂-O-CH₂-, -CH₂-N(alkyl)-CH₂-, -CH₂-N(aryl)-CH₂-, -OCH₂CH₂O-, -OCH₂CH₂OCH₂CH₂O-, or -OCH₂CH₂OCH₂CH₂OCH₂CH₂O-. Unless stated otherwise specifically in the specification, a heteroalkyl is optionally substituted for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heteroalkyl is optionally substituted with halogen.

[055] The term “heterocycloalkyl” refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen, and sulfur. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical may be a monocyclic, or bicyclic ring system, which may include fused (when fused with an aryl or a heteroaryl ring, the heterocycloalkyl is bonded through a non-aromatic ring atom) or bridged ring systems. The nitrogen, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized. The nitrogen atom may be optionally quaternized. The heterocycloalkyl radical is partially or fully saturated. Examples of

heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, decahydroisoquinolyl, imidazolyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranlyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl. The term heterocycloalkyl also includes all ring forms of carbohydrates, including but not limited to monosaccharides, disaccharides and oligosaccharides. Unless otherwise noted, heterocycloalkyls have from 2 to 12 carbons in the ring. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring and 1 or 2 N atoms. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring and 3 or 4 N atoms. In some embodiments, heterocycloalkyls have from 2 to 12 carbons, 0-2 N atoms, 0-2 O atoms, 0-2 P atoms, and 0-1 S atoms in the ring. In some embodiments, heterocycloalkyls have from 2 to 12 carbons, 1-3 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e., skeletal atoms of the heterocycloalkyl ring). Unless stated otherwise specifically in the specification, a heterocycloalkyl is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heterocycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a heterocycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heterocycloalkyl is optionally substituted with halogen.

[056] “Heteroaryl” refers to a ring system radical comprising carbon atom(s) and one or more ring heteroatoms that selected from the group consisting of nitrogen, oxygen, phosphorous, and sulfur, and at least one aromatic ring. In some embodiments, heteroaryl is monocyclic, bicyclic or polycyclic. Illustrative examples of monocyclic heteroaryls include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, furazanyl, indolizine, indole, benzofuran, benzothiophene, indazole, benzimidazole, purine, quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, and pteridine. Illustrative examples of monocyclic heteroaryls include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl,

oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl. Illustrative examples of bicyclic heteroaryls include indolizine, indole, benzofuran, benzothiophene, indazole, benzimidazole, purine, quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, and pteridine. In some embodiments, heteroaryl is pyridinyl, pyrazinyl, pyrimidinyl, thiazolyl, thienyl, thiadiazolyl or furyl. In some embodiments, a heteroaryl contains 0-6 N atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms in the ring. In some embodiments, a heteroaryl contains 4-6 N atoms in the ring. In some embodiments, a heteroaryl contains 0-4 N atoms, 0-1 O atoms, 0-1 P atoms, and 0-1 S atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. In some embodiments, heteroaryl is a C₁-C₉ heteroaryl. In some embodiments, monocyclic heteroaryl is a C₁-C₅ heteroaryl. In some embodiments, monocyclic heteroaryl is a 5-membered or 6-membered heteroaryl. In some embodiments, a bicyclic heteroaryl is a C₆-C₉ heteroaryl. In some embodiments, a heteroaryl group comprises a partially reduced cycloalkyl or heterocycloalkyl group defined herein (e.g., 7,8-dihydroquinoline). In some embodiments, a heteroaryl group comprises a fully reduced cycloalkyl or heterocycloalkyl group defined herein (e.g., 5,6,7,8-tetrahydroquinoline). When heteroaryl comprises a cycloalkyl or heterocycloalkyl group, the heteroaryl is bonded to the rest of the molecule through a heteroaromatic ring carbon or hetero atom. A heteroaryl radical can be a monocyclic or polycyclic (e.g., bicyclic, tricyclic, or tetracyclic) ring system, which may include fused, spiro or bridged ring systems. Unless stated otherwise specifically in the specification, a heteroaryl is optionally substituted, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heteroaryl is optionally substituted with halogen.

[057] The term “moiety” refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[058] The terms “treat,” “prevent,” “ameliorate,” and “inhibit,” as well as words stemming therefrom, as used herein, do not necessarily imply 100% or complete treatment, prevention, amelioration, or inhibition. Rather, there are varying degrees of treatment, prevention, amelioration, and inhibition of which one of ordinary skill in the art recognizes as having a potential benefit or therapeutic effect. In this respect, the disclosed methods can provide any amount of any level of treatment, prevention, amelioration, or inhibition of the disorder in a mammal. For example, a disorder, including symptoms or conditions thereof, may be reduced by,

for example, about 100%, about 90%, about 80%, about 70%, about 60%, about 50%, about 40%, about 30%, about 20%, or about 10%. Furthermore, the treatment, prevention, amelioration, or inhibition provided by the methods disclosed herein can include treatment, prevention, amelioration, or inhibition of one or more conditions or symptoms of the disorder, e.g., cancer or an inflammatory disease. Also, for purposes herein, "treatment," "prevention," "amelioration," or "inhibition" encompass delaying the onset of the disorder, or a symptom or condition thereof. As used herein, "treating" includes the concepts of "alleviating", which refers to lessening the frequency of occurrence or recurrence, or the severity, of any symptoms or other ill effects related to a disorder and/or the associated side effects. The term "treating" also encompasses the concept of "managing" which refers to reducing the severity of a particular disease or disorder in a patient or delaying its recurrence, e.g., lengthening the period of remission in a patient who had suffered from the disease.

[059] The term "therapeutically effective amount" as used herein to refer to an amount effective at the dosage and duration necessary to achieve the desired therapeutic result. A therapeutically effective amount of the composition may vary depending on factors such as the individual's condition, age, sex, and weight, and the ability of the protein to elicit the desired response of the individual. A therapeutically effective amount can also be an amount that exceeds any toxic or deleterious effect of the composition that would have a beneficial effect on the treatment.

[060] The term "optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted alkyl" means either "alkyl" or "substituted alkyl" as defined above. Further, an optionally substituted group may be un-substituted (e.g., -CH₂CH₃), fully substituted (e.g., -CF₂CF₃), mono-substituted (e.g., -CH₂CH₂F) or substituted at a level anywhere in-between fully substituted and mono-substituted (e.g., -CH₂CHF₂, -CH₂CF₃, -CF₂CH₃, -CFHCHF₂, etc.).

[061] As used herein, the term "substituent" means positional variables on the atoms of a core molecule that are substituted at a designated atom position, replacing one or more hydrogens on the designated atom, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. A person of ordinary skill in the art should note that any carbon as well as heteroatom with valences that appear to be unsatisfied as described or shown herein is assumed to have a sufficient number of hydrogen atom(s) to satisfy the valences described or shown. In certain instances one or more substituents having a double bond (e.g., "oxo" or "=O") as the point of attachment may be described, shown or listed herein within a substituent group, wherein the structure may only show a single bond as

the point of attachment to the core structure. A person of ordinary skill in the art would understand that, while only a single bond is shown, a double bond is intended for those substituents.

[062] The term “optionally substituted” or “substituted” means that the referenced group is optionally substituted with one or more additional group(s) individually and independently selected from D, halogen, -CN, oxo, -NH₂, -NH(alkyl), -N(alkyl)₂, -OH, -CO₂H, -CO₂alkyl, -C(=O)NH₂, -C(=O)NH(alkyl), -C(=O)N(alkyl)₂, -S(=O)₂NH₂, -S(=O)₂NH(alkyl), -S(=O)₂N(alkyl)₂, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some embodiments, optional substituents are independently selected from D, halogen, -CN, oxo, -NH₂, -NH(CH₃), -N(CH₃)₂, -OH, -CO₂H, -CO₂(C₁-C₄alkyl), -C(=O)NH₂, -C(=O)NH(C₁-C₄alkyl), -C(=O)N(C₁-C₄alkyl)₂, -S(=O)₂NH₂, -S(=O)₂NH(C₁-C₄alkyl), -S(=O)₂N(C₁-C₄alkyl)₂, C₁-C₄alkyl, C₃-C₆cycloalkyl, C₁-C₄fluoroalkyl, C₁-C₄heteroalkyl, C₁-C₄alkoxy, C₁-C₄fluoroalkoxy, -SC₁-C₄alkyl, -S(=O)C₁-C₄alkyl, and -S(=O)₂C₁-C₄alkyl. In some embodiments, optional substituents are independently selected from D, halogen, -CN, -NH₂, -OH, -NH(CH₃), -N(CH₃)₂, -NH(cyclopropyl), -CH₃, -CH₂CH₃, -CF₃, -OCH₃, and -OCF₃. In some embodiments, substituted groups are substituted with one or two of the preceding groups. When indicating the number of substituents, the term “one or more” means from one substituent to the highest possible number of substitutions, i.e. replacement of one hydrogen up to replacement of all hydrogens by substituents.

[063] The term “unsubstituted” means that the specified group bears no substituents.

[064] Certain compounds described herein may exist in tautomeric forms, and all such tautomeric forms of the compounds being within the scope of the disclosure.

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

[066] The term “peptide” as used herein refers to a compound that includes two or more amino acids. A peptide described herein can comprise one or more unnatural amino acids. The term “peptide” also encompasses peptide mimetics. In the present disclosure, the term “amino acid” is used in its broadest meaning and it embraces not only natural amino acids but also derivatives thereof and artificial amino acids. For example, the term “amino acid” encompasses unnatural amino acids.

[067] As used herein, the term “unnatural amino acid” refers to an amino acid other than the 20 amino acids that occur naturally in protein.

[068] The term “protein” as used herein refers to a polypeptide (i.e., a string of at least 3 amino acids linked to one another by peptide bonds). Proteins can include moieties other than amino acids (e.g., may be glycoproteins, proteoglycans, etc.) and/or can be otherwise processed or modified. A protein can be a complete polypeptide as produced by and/or active in a cell (with or without a signal sequence). In some embodiments, a protein is or comprises a characteristic portion such as a polypeptide as produced by and/or active in a cell. A protein can include more than one polypeptide chain.

[069] The term “peptide mimetic” or “mimetic” refers to biologically active compounds that mimic the biological activity of a peptide or a protein but are no longer entirely peptidic in chemical nature, e.g., they can contain non-peptide bonds (that are, bonds other than amide bonds between amino acids). As used herein, the term peptide mimetic is used in a broader sense to include molecules that are no longer completely peptidic in nature, such as pseudo-peptides, semi-peptides and peptoids. Whether completely or partially non-peptide, peptide mimetics described herein can provide a spatial arrangement of reactive chemical moieties that closely resemble the three-dimensional arrangement of active groups in the subject amino acid sequence or subject molecule on which the peptide mimetic is based. As a result of this similar active-site geometry, the peptide mimetic can have effects on biological systems that are similar to the biological activity of the subject entity.

[070] In some embodiments, the peptide mimetics are substantially similar in both three-dimensional shape and biological activity to the subject amino acid sequence or subject molecule on which the peptide mimetic is based. Examples of methods of structurally modifying a peptide to create a peptide mimetic include the inversion of backbone chiral centers leading to D-amino acid residue structures that may, particularly at the N-terminus, lead to enhanced stability for proteolytical degradation without adversely affecting activity. An example is described in the paper “Tritiated D-ala1-Peptide T Binding”, Smith C. S. et al., *Drug Development Res.*, 15, pp. 371-379 (1988). A second method is altering cyclic structure for stability, such as N to C interchain imides and lactames (Ede et al. in Smith and Rivier (Eds.) “Peptides: Chemistry and Biology”, Escom, Leiden (1991), pp. 268-270). An example of this is provided in conformationally restricted thymopentin-like compounds, such as those disclosed in US4457489. A third method is to substitute peptide bonds in the subject entity by pseudopeptide bonds that confer resistance to proteolysis.

[071] Ranges provided herein are understood to be shorthand for all of the values within the range. For example, a range of 1 to 50 is understood to include any number, combination of numbers, or sub-range from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41,

42, 43, 44, 45, 46, 47, 48, 49, or 50, as well as all intervening decimal values between the aforementioned integers such as, for example, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, and 1.9. With respect to sub-ranges, “nested sub-ranges” that extend from either end point of the range are specifically contemplated. For example, a nested sub-range of an exemplary range of 1 to 50 may comprise 1 to 10, 1 to 20, 1 to 30, and 1 to 40 in one direction, or 50 to 40, 50 to 30, 50 to 20, and 50 to 10 in the other direction.

[072] As used herein, C₁-C_x (or C_{1-x}) includes C₁-C₂, C₁-C₃... C₁-C_x. By way of example only, a group designated as “C₁-C₄” indicates that there are one to four carbon atoms in the moiety, i.e., groups containing 1 carbon atom, 2 carbon atoms, 3 carbon atoms or 4 carbon atoms. Thus, by way of example only, “C₁-C₄ alkyl” indicates that there are one to four carbon atoms in the alkyl group, i.e., the alkyl group is selected from among methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl. Also, by way of example, C₀-C₂ alkylene includes a direct bond, -CH₂-, and -CH₂CH₂- linkages.

[073] The term “cyclized” or “cyclization” as used herein means that two amino acids apart from each other by at least one amino acid bind directly or bind indirectly to each other in one peptide to form a cyclic structure in the molecule. In some cases, the two amino acids bind via a linker or the like.

[074] The term “subject” or “patient” encompasses mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In one aspect, the mammal is a companion animal such as a dog or a cat. In one aspect, the mammal is a human.

[075] The term “therapeutically effective amount” as used herein to refer to an amount effective at the dosage to achieve the desired therapeutic result. A therapeutically effective amount of a composition may vary depending on factors such as the individual's condition (e.g., age, sex, and weight), the radiopharmaceutical conjugate, and the method of administration (e.g., oral or parenteral).

II. Technical Overview

[076] Targeted Radiopharmaceuticals (TRP) are a new generation of nuclear medicine for cancer treatment or diagnosis. A TRP can selectively deliver high concentrations of radionuclide-containing molecules to the target cells such as a tumor, and no or very low concentrations to the undesired cells present in normal, healthy tissues. The process can be achieved by engineering the drug molecule with the high-affinity binder (e.g., targeting ligands) and linking it to the radioactive isotope. The biological targets of these binders are highly expressed on tumor cells and have low

or no expression in healthy tissues and organs. When the radioisotope decays, it emits highly energetic ionizing radiation in form of alpha, beta, and/or gamma particles. The released energy at the target sites can cause damage or death of the target tissues or be visualized by imaging scanner to achieve therapeutic or diagnostic purposes.

[077] In some traditional radiopharmaceutical formulations, a very high concentration of stabilizer as to radiopharmaceutical is used. The high concentration can produce unknown biological effects and/or compromise therapeutic efficacy of the radiopharmaceutical. Due to the low efficiency of those stabilizers used in the past, significant dilution was needed to slow down the decomposition. As a result, larger volume of dose can require treatment via infusion instead of bolus injection under clinical setting. This is less desired for patients due to the prolonged stay at the infusion center and sometimes hospitalization. One of the major challenges in the production of radiopharmaceutical drugs is to extend the shelf-life of product to allow treatment of patients at remote locations from the manufacturer site. Increasing stability of radiopharmaceutical drug in formulated solution can resolve this challenge.

[078] In some cases, with decay of the parent isotopes, daughter isotopes can be released into the solution. They can be non-radioactive or radioactive. When the daughter ions are radioactive, those non-bonded ions can create non-specific distribution of radioactivity in vivo and generate undesired toxicities. In addition, even if they are not radioactive, they can still bind to the metal chelation moiety on the radiopharmaceutical drug due to their higher affinity. The replacement of their parent ions can cause chemical decomposition of the drug substance. This process can also negatively impact the radiochemical purities overtime. When decay of Actinium-225-DOTA-containing drug starts, the isotope can first decay into Francium-221(I). The recoil energy of the process can be approximately 10000 times higher than any known chemical bond energy. It can cause the daughter ions to escape from their original chelator (e.g., DOTA). Due to the chemical nature of Francium-221 (I), in some cases, they cannot be recaptured by free DOTA-containing drug. As decay continues, more free daughter ions can enter the solution. Eventually, the majority of the decayed daughters can accumulate in the form of stable Bismuth-209 (III). Bismuth-209 (III) can be strongly chelated with DOTA and compete with Ac-225 for binding to the parent drug, leading to further dissociation of Ac-225 from its chelator and generating additional radioactive free (unchelated) metal impurities.

[079] The decay of radionuclides can be accompanied by emission of energy in the form of alpha, beta and/or gamma radiations. The energy can go into the radiopharmaceutical-containing solution and can break chemical bonds, generate reactive chemical species from solvent molecules, and further decompose the radiopharmaceutical drug directly or indirectly. This process can be referred to as radiolysis. Radiolysis can be particularly severer when a concentrated

radioactive compound is present in small volume of solution. In the case of Actinium-225-DOTA-containing radiopharmaceuticals, Actinium-225 can decay into Francium-221, Astatine-217, Bismuth-213, Thallium-209, Polonium-213, Lead-209, and Bismuth-209 in sequence. The decay chain can contain four alpha particle emissions and two beta particle emissions. In addition, Francium-221 and Bismuth-213 can release up to 25% of their decay energy through gamma emission. The ionizing radiation can cause radiolysis of surrounding water molecules particularly produce $\text{H}^\cdot$ atoms, $\cdot\text{OH}$ radicals, H_3O^+ ions and oxidizing agent hydrogen peroxide. These chemical species can be highly reactive. In some cases, they can react with the drug substance, cause degradation of the radioisotope-containing peptide drug, and increase radioactive impurity overtime.

[080] Accordingly, provided herein are radiopharmaceutical compositions with improved stability, for example, compositions containing Actinium-225.

[081] In one aspect, the present disclosure relates to a radionuclide solution with radioisotopes and its daughter ions. The solution composition can comprise ingredients which stabilize the radioactive drug substance from radiolysis and chemical decomposition. The increased stability of the drug substance can extend shelf-life of radiopharmaceuticals, as such to achieve their wide applications as a drug product for their diagnostic and therapeutic purpose.

[082] In one aspect, the compositions described herein have increased stability of the radiopharmaceutical conjugate. The radiopharmaceutical composition can contain ingredients, such as radiopharmaceutical stabilizers, which stabilize the radioactive drug substance from radiolysis and chemical decomposition. The radiopharmaceuticals stabilizers can comprise reducing agents and/or radical scavengers, such as ascorbic acid to reduce the radiolysis. The composition of the present disclosure can have extended shelf-life. The compositions described herein can comprise one or more stabilizing agents. The stabilizing agents can prevent or delay radiolysis of the radiopharmaceutical conjugate. The stabilizing agents can prevent or delay decomposition of the radiopharmaceutical conjugate. The stabilizing agents can prevent or delay chemical decomposition of the radiopharmaceutical conjugate caused by radioactive decay-generated daughter ions. The stabilizing agents can prevent or delay chemical decomposition of the radiopharmaceutical conjugate caused by pH changes. The stabilizing agents can be added into the composition at a low concentration. The stabilizing agents can be optionally added into the composition at a low concentration. The increased stability of the radiopharmaceutical conjugate can achieve one or more applications in the field of medicine. The applications can comprise acting as a drug product for one or more diagnostic purposes. The applications can comprise acting as a drug product for one or more therapeutic purposes. A treatment plan for a patient or subject receiving the radiopharmaceutical compositions described herein can include

treatment at remote locations. A treatment plan for a patient or subject receiving the radiopharmaceutical compositions described herein can include a shorter stay at the infusion center or at the hospital.

[083] A radiopharmaceutical conjugate can comprise a radionuclide and a metal chelator. The radionuclide and the metal chelator can be linked by ionic and coordinate bonding. The radionuclides for therapeutic purpose can include Lutetium-177, Actinium-225, Yttrium-90, and Bismuth-213. The radionuclides for diagnostic purpose can include Gallium-68, Copper-64, and Indium-111. The chelator can further bind to a target binder, such as one that has a high-affinity with the target of the radiopharmaceutical conjugate, directly or via a linker covalently. Exemplary metal chelators can include aza-crown ether-based polycarboxylic acid such as 2,2',2'',2'''-(1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetrayl)tetraacetic acid (DOTA), or 1,4,7-Triazacyclononane-1,4,7-triacetic acid (NOTA). The chelation can keep the radionuclide from releasing into surroundings in vitro and/or in vivo.

III. Compositions

[084] In one aspect, the present disclosure provides liquid radiopharmaceutical compositions comprising a radiopharmaceutical conjugate. The conjugate can comprise a targeting ligand. The targeting ligand can be a binding peptide or a chemical group or small molecule. The conjugate can further comprise a chelator such as a metal chelator. The chelator can be covalently attached to the targeting ligand. The conjugate can further comprise a radionuclide. In some embodiments, the radionuclide is bound to the chelator. The composition can further comprise one or more stabilizing agents. The one or more stabilizing agents are agents that can stabilize the composition or formulation of the radiopharmaceutical conjugates. The one or more stabilizing agents can reduce or delay the decomposition of the radiopharmaceutical conjugates in the composition.

[085] In one aspect, provided herein are liquid radiopharmaceutical compositions comprising ^{225}Ac -DOTATATE. In one aspect, provided herein are liquid radiopharmaceutical compositions comprising ^{225}Ac -DOTATOC. In one aspect, provided herein are liquid radiopharmaceutical compositions comprising ^{225}Ac -DOTA-JR-11. In one aspect, provided herein are liquid radiopharmaceutical compositions comprising ^{225}Ac -HA-DOTA-TATE.

[086] In one aspect, disclosed herein is a radiopharmaceutical composition, comprising: (a) the conjugate, wherein the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 1 to about 100 mCi/L (e.g., about 10 to about 50 mCi/L, about 5 to about 50 mCi/L); (b) a pH stabilizer, wherein the pH stabilizer is present in the radiopharmaceutical composition at a concentration of about 50 to about 500 mM (e.g., about 80 to about 120 mM, about 50 to 200 mM); (c) optionally a radiolysis stabilizer, wherein the radiolysis stabilizer is present in the radiopharmaceutical composition at concentration of about 1

wt% to about 10wt%; (d) a free metal chelator, wherein the free metal chelator is present in the radiopharmaceutical composition at concentration of about 0.01 mg/mL to about 5 mg/mL (e.g., about 0.01 mg/mL to about 1 mg/mL); and (e) an aqueous vehicle.

[087] In one aspect, disclosed herein is a radiopharmaceutical composition, comprising: (a) the conjugate, wherein the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 1 to 50 mCi/L; (b) a radiolysis stabilizer, wherein the radiolysis stabilizer is ascorbic acid or a salt thereof (e.g., sodium L-ascorbate) and is present in the radiopharmaceutical composition at a concentration of about 50 mM to about 1500 mM (e.g., about 80 to about 120 mM, about 80 to about 500 mM, about 50 mM to about 200 mM); (c) a free metal chelator, wherein the free metal chelator is selected from EDTA, macropa, TETA, PEPA, TETPA, DFO, DOPT, DHLA, TGA, LA, and DTPA, or a combination thereof, and wherein the free metal chelator is present in the radiopharmaceutical composition at a concentration of about 0.01 mg/mL to about 5 mg/mL (e.g., about 0.01 mg/mL to about 1 mg/mL, about 0.01 mg/mL to about 2.5 mg/mL); and (d) an aqueous vehicle, wherein the aqueous vehicle is saline solution. In some embodiments, the radiopharmaceutical composition further comprises a pH stabilizer. In some embodiments, the radiolysis stabilizer functions as a pH stabilizer. In some embodiments, the radiopharmaceutical composition further comprises a second radiolysis stabilizer. In some embodiments, the second radiolysis stabilizer (e.g., Dextran 40) is present in the radiopharmaceutical composition at a concentration of about 1 wt% to about 10wt%. In some embodiments, the second radiolysis stabilizer is present in the radiopharmaceutical composition at a concentration of about 0.05 wt% to about 5 wt%. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 5 to 50 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 to 50 mCi/L. In some embodiments, a radiopharmaceutical composition comprise a pH stabilizer that is present in the formulation at about 80 to about 500 mM. In some embodiments, a radiopharmaceutical composition comprise a pH stabilizer that is present in the formulation at about 50 mM to about 200 mM. In some embodiments, a radiopharmaceutical composition comprise a pH stabilizer that is present in the formulation at about 25 mM to about 300 mM. In some embodiments, a radiopharmaceutical composition comprise a free metal chelator that is present in the formulation at about 0.01 mg/mL to about 1 mg/mL. In some embodiments, a radiopharmaceutical composition comprise a free metal chelator that is present in the formulation at about 0.02 mg/mL to about 3 mg/mL. In some embodiments, a radiopharmaceutical composition comprise a free metal chelator that is present in the formulation at about 0.02 mg/mL to about 2 mg/mL.

[088] In one aspect, disclosed herein is a radiopharmaceutical composition, comprising: (a) the conjugate, wherein the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 1 to 50 mCi/L; (b) optionally, a pH stabilizer, wherein the pH stabilizer is configured to maintain a pH of the radiopharmaceutical composition at about 4 to 8; (c) a radiolysis stabilizer; (d) a free metal chelator, wherein the free metal chelator is configured to maintain a level of free radionuclide in the radiopharmaceutical composition below about 0.05 mCi/L; and (e) an aqueous vehicle. In some embodiments, the radiolysis stabilizer (such as ascorbic acid or sodium ascorbate) can function as a pH stabilizer. In some embodiments, the radiolysis stabilizer and the pH stabilizer is the same compound. In some embodiments, the free metal chelator is configured to maintain a level of free radionuclide in the radiopharmaceutical composition below about 0.05 mCi/L for at least 72 hours at about at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC). In some embodiments, the free metal chelator is configured to maintain a level of free radionuclide in the radiopharmaceutical composition below about 0.2, about 0.2, about 0.01 or about 0.001 mCi/L for at least 72 hours at about at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC). In some embodiments, the free metal chelator is configured to maintain a level of free radionuclide in the radiopharmaceutical composition below about 0.2, about 0.2, about 0.01 or about 0.001 mCi/L for at least 168 hours at about at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC). In some embodiments, the free radionuclide is unbound or unchelated ²²⁵Ac. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 5 to 50 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 to 50 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 mCi/L to about 15 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 mCi/L.

[089] In some embodiments, a radiopharmaceutical composition described herein retains at least 90 % of the ²²⁵Ac content bound as part of the conjugate after 72 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC). In some embodiments, a radiopharmaceutical composition described herein retains at least 90 % of the ²²⁵Ac content bound as part of the conjugate after 120 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC). In some embodiments, a radiopharmaceutical composition described herein retains at least 95 % of the ²²⁵Ac content bound as part of the conjugate after 120 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC). In some embodiments, a radiopharmaceutical composition described herein retains at least 90 %

of the ^{225}Ac content bound as part of the conjugate after 120 hours at about 20°C to about 25°C as determined by high performance liquid chromatography/fraction collection (HPLC-FC). In some embodiments, a radiopharmaceutical composition described herein retains at least 90 % of the ^{225}Ac content bound as part of the conjugate after 72 hours at about 20°C to about 25°C as determined by high performance liquid chromatography/fraction collection (HPLC-FC). In some embodiments, a radiopharmaceutical composition described herein retains at least 95 % of the ^{225}Ac content bound as part of the conjugate after 72 hours at about 20°C to about 25°C as determined by high performance liquid chromatography/fraction collection (HPLC-FC). In some embodiments, a radiopharmaceutical composition described herein retains at least 90 % of the ^{225}Ac content bound as part of the conjugate after 168 hours at about 20°C to about 25°C as determined by high performance liquid chromatography/fraction collection (HPLC-FC). In some embodiments, a radiopharmaceutical composition described herein retains at least 95 % of the ^{225}Ac content bound as part of the conjugate after 168 hours at about 20°C to about 25°C as determined by high performance liquid chromatography/fraction collection (HPLC-FC).

[090] In one aspect, disclosed herein is a liquid radiopharmaceutical composition comprising: (a) a conjugate that comprises (i) a targeting ligand, wherein the targeting ligand binds to a somatostatin receptor (SSR), (ii) a metal chelator covalently attached to the targeting ligand, and (iii) a radionuclide, wherein the radionuclide is ^{225}Ac , (b) a means for maintaining a pH of the radiopharmaceutical composition, wherein the pH of the radiopharmaceutical composition is about 4 to about 8; (c) a means for scavenging free radionuclide in the radiopharmaceutical composition; and (d) an aqueous vehicle. In some embodiments, wherein the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content as part of the radionuclide after 120 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC). In some embodiments, the means for scavenging free radionuclide is a free metal chelator described herein. In some embodiments, the means for maintaining a pH of the radiopharmaceutical composition is a pH stabilizer described herein. In some embodiments, the liquid radiopharmaceutical composition is a solution. In one aspect, disclosed herein is a liquid radiopharmaceutical composition comprising: (a) a conjugate that comprises (i) a targeting ligand, wherein the targeting ligand binds to a somatostatin receptor (SSR), (ii) a metal chelator covalently attached to the targeting ligand, and (iii) a radionuclide, wherein the radionuclide is ^{225}Ac , wherein the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 0.1 mCi/L to about 50 mCi/L; (b) a pH stabilizer; (c) a free metal chelator; and (d) an aqueous vehicle. In some embodiments, the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content as part of the radionuclide after 120 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC). In some embodiments, the liquid

radiopharmaceutical composition is a solution. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 mCi/L to about 35 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 1 mCi/L to about 50 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 mCi/L to about 50 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 5 mCi/L to about 35 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 mCi/L to about 15 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 mCi/L to about 25 mCi/L. In some embodiments, the conjugate is ^{225}Ac -DOTA-TATE, ^{225}Ac -DOTA-TOC, or ^{225}Ac -DOTA-JR-11. In some embodiments, the conjugate is ^{225}Ac -HA-DOTA-TATE. In some embodiments, the pH stabilizer is ascorbic acid, a salt thereof, or a combination thereof. In some embodiments, the pH stabilizer is present in the radiopharmaceutical composition at a concentration of about 50 mM to about 200 mM. In some embodiments, the free metal chelator is selected from EDTA, macropa, TETA, PEPA, TETPA, DFO, DOPT, DHLA, TGA, LA, and DTPA, or a combination thereof. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at a concentration of about 0.01mg/mL to about 5 mg/mL. In some embodiments, the conjugate is ^{225}Ac -DOTA-TATE and the composition retains at least 90 % of the ^{225}Ac content as ^{225}Ac -DOTA-TATE after 168 hours at about 20°C to about 25°C. In some embodiments, the conjugate is ^{225}Ac -DOTA-TATE and the composition retains at least 95 % of the ^{225}Ac content as ^{225}Ac -DOTA-TATE after 168 hours at about 20°C to about 25°C. In some embodiments, the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content bound as part of the conjugate after 120 hours at about 20°C to about 25°C as determined by high performance liquid chromatography/fraction collection (HPLC-FC). In some embodiments, the radiopharmaceutical composition is formulated as a unit dose form that contains about 5 ml to about 50 ml (e.g., about 10-15 ml, about 12mL) of the solution. In some embodiments, the aqueous vehicle is a saline solution.

[091] The liquid radiopharmaceutical compositions can comprise pharmaceutically acceptable carriers or diluents. Exemplary pharmaceutically acceptable carriers include solvents (aqueous or non-aqueous), solutions, emulsions, dispersion media, coatings, isotonic and absorption promoting or delaying agents, compatible with pharmaceutical administration. In some embodiments, the liquid radiopharmaceutical compositions described herein are formulated as a

solution, emulsion, suspension, syrup, elixir, or the like. The compositions can be aqueous radiopharmaceutical compositions.

[092] The liquid radiopharmaceutical composition can comprise an aqueous vehicle. For example, the aqueous vehicle can comprise water, saline solution, dextrose in water, dextrose in saline solution, Ringer's solution, or lactated Ringer's solution. In some embodiments, the aqueous vehicle is water. In some embodiments, the aqueous vehicle is water for injection. In some embodiments, the aqueous vehicle is 5.0% w/w sodium chloride solution. In some embodiments, the aqueous vehicle is 4.0% w/w sodium chloride solution. In some embodiments, the aqueous vehicle is 3.0% sodium chloride solution. In some embodiments, the aqueous vehicle is 2.0% w/w sodium chloride solution. In some embodiments, the aqueous vehicle is 1.5% w/w sodium chloride solution. In some embodiments, the aqueous vehicle is 1.0% sodium chloride solution. In some embodiments, the aqueous vehicle is 0.9% w/w sodium chloride saline solution. In some embodiments, the aqueous vehicle is 0.5% w/w sodium chloride solution. In some embodiments, the aqueous vehicle is 0.5% to 1.5% w/w sodium chloride solution. In some embodiments, the aqueous vehicle is 0.7% to 1.1% w/w sodium chloride solution. In some embodiments, the aqueous vehicle is saline solution. In some embodiments, the aqueous vehicle is dextrose in water. In some embodiments, the aqueous vehicle is dextrose in saline solution. The compositions can be isotonic. The composition can be a solution or suspension. In some embodiments, the liquid radiopharmaceutical is formulated as a solution. The compositions can be formulated to be compatible with a particular local or systemic route of administration. The compositions can include carriers, diluents, or excipients suitable for administration by particular routes. The composition can be formulated for IV infusion or bolus injection. In some embodiments, the liquid radiopharmaceutical is formulated for intravenous administration.

[093] Supplementary components or excipients can also be incorporated into the liquid radiopharmaceutical compositions. The composition can further comprise one or more supplementary components or excipients. The supplementary components or excipients can be preservatives, antibacterial, antiviral, antimicrobial and/or antifungal agents. The supplementary components or excipients can be a tonicity adjusting agent, a solubilizing agent, a suspending agent, and/or a surfactant.

[094] The liquid radiopharmaceutical compositions described herein can be storage stable for a period of time. In some embodiments, the liquid radiopharmaceutical compositions described herein retain at least 80 mol% of the initial conjugate after 168 hours at room temperature. In some embodiments, the compositions retain at least 85 mol% of the initial conjugate after 168 hours at room temperature. In some embodiments, the compositions retain at least 90 mol% of the initial conjugate after 168 hours at room temperature. In some embodiments, the compositions

retain at least 95 mol% of the initial conjugate after 168 hours at room temperature. In some embodiments, the compositions described retain at least 98 mol% of the initial conjugate after 168 hours at room temperature. In some embodiments, the composition retains at least 85 mol%, at least 90 mol%, at least 92 mol%, at least 95 mol%, at least 98 mol% or at least 99 mol% of the initial conjugate after 120 hours at room temperature. In some embodiments, the composition retains at least 85 mol%, at least 90 mol%, at least 92 mol%, at least 95 mol%, at least 98 mol% or at least 99 mol% of the initial conjugate after 96 hours at room temperature. In some embodiments, the composition retains at least 85 mol%, at least 90 mol%, at least 92 mol%, at least 95 mol%, at least 98 mol% or at least 99 mol% of the initial conjugate after 48 hours at room temperature. In some embodiments, the compositions described herein retain at least 85 mol%, at least 90 mol%, at least 92 mol%, at least 95 mol%, at least 98 mol% or at least 99 mol% of the initial conjugate after 2 weeks at refrigerated condition (about 4°C). In some embodiments, the compositions described herein retain at least 85 mol%, at least 90 mol%, at least 92 mol%, at least 95 mol%, at least 98 mol%, at least 99 mol%, or at least 99.5 mol% of the initial conjugate after 168 hours at refrigerated condition (about 4°C). In some embodiments, the compositions described herein retain at least 85 mol%, at least 90 mol%, at least 92 mol%, at least 95 mol%, at least 98 mol%, at least 99 mol%, or at least 99.5 mol% of the initial conjugate after 96 hours at refrigerated condition (about 4°C). In some embodiments, the compositions described herein retain at least 85 mol%, at least 90 mol%, at least 92 mol%, at least 95 mol%, at least 98 mol%, at least 99 mol%, or at least 99.5 mol% of the initial conjugate after 48 hours at refrigerated condition (about 4°C). In some embodiments, the purity or the molar percentage of the conjugate is determined by radio thin layer chromatography (radio-TLC). In some embodiments, the purity or the molar percentage of the conjugate is determined by instant thin layer chromatography (iTLC). In some embodiments, the purity or the molar percentage of the conjugate is determined by measuring the related α -particle emission using radio-TLC.

[095] The liquid radiopharmaceutical compositions described herein can retain an amount of the initial conjugate (such as ^{225}Ac -DOTA-TATE) after stored for a period of time. In some embodiments, the radiopharmaceutical composition retains 95 mol% or more of the initial conjugate after 48 hours, 72 hours, 96 hours, 120 hours, 148 hours, 168 hours, 192 hours, or 216 hours at room temperature. In some embodiments, the radiopharmaceutical composition retains 95 mol% or more of the initial conjugate after 96 hours at room temperature. In some embodiments, the radiopharmaceutical composition retains 95 mol% or more of the initial

conjugate after 120 hours at room temperature. In some embodiments, the radiopharmaceutical composition retains 95 mol% or more of the initial conjugate after 148 hours at room temperature. In some embodiments, the radiopharmaceutical composition retains 95 mol% or more of the initial conjugate after 168 hours at room temperature. In some embodiments, the radiopharmaceutical composition retains 95 mol% or more of the initial conjugate after 192 hours at room temperature. In some embodiments, the purity or the molar percentage of the conjugate is determined by instant thin-layer chromatography (iTLC). In some embodiments, the purity or the molar percentage of the conjugate is determined by radio thin-layer chromatography (radio-TLC). In some embodiments, room temperature can refer to a temperature of about 25°C. In some embodiments, room temperature can refer to a temperature of 25°C. In some embodiments, room temperature can refer to a temperature of about 22°C to about 25°C. In some embodiments, room temperature can refer to a temperature of about 20°C to about 25°C.

[096] The liquid radiopharmaceutical compositions described herein can contain a small amount of the unchelated and un-conjugated radionuclide after stored for a period of time. In some embodiments, the liquid radiopharmaceutical compositions described herein contain a small amount of free actinium-225 and actinium-225 present in a fragment of the conjugate ^{225}Ac -DOTA-TATE (e.g., as ^{225}Ac -DOTA fragment) after being stored for a period of time. For example, see Example 3. The total content of the radionuclide such as actinium-225 in the radiopharmaceutical composition can also decrease over time due to the decay of the radionuclide. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than about 20% free actinium-225 after 120 hours at about 20°C to 25°C, compared to the total amount of the actinium-225 content in the composition (at that time of measurement). In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than about 10% free actinium-225 after 120 hours at about 20°C to 25°C, compared to the total amount of the actinium-225 content in the composition. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than about 5% free actinium-225 after 120 hours at about 20°C to 25°C, compared to the total amount of the actinium-225 content in the composition. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than about 2% free actinium-225 after 120 hours at about 20°C to 25°C, compared to the total amount of the actinium-225 content in the composition. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than about 1% free actinium-225 after 120 hours at about 20°C to 25°C, compared to the total amount of the actinium-225 content in the composition.

[097] In some embodiments, after being stored for 120 hours at about 20°C to about 25°C, at least 90 mol% of the ^{225}Ac (i.e., actinium-225) content in the liquid radiopharmaceutical composition (at that time of measurement) is present as ^{225}Ac -DOTA-TATE. In some embodiments, after being stored for 120 hours at about 20°C to about 25°C, at least 95 mol% of the ^{225}Ac (i.e., actinium-225) content in the liquid radiopharmaceutical composition is present as ^{225}Ac -DOTA-TATE. In some embodiments, after being stored for 120 hours at about 20°C to about 25°C, at least 98 mol% of the ^{225}Ac (i.e., actinium-225) content in the liquid radiopharmaceutical composition is present as ^{225}Ac -DOTA-TATE. In some embodiments, after being stored for 120 hours at about 20°C to about 25°C, at least 99 mol% of the ^{225}Ac (i.e., actinium-225) content in the liquid radiopharmaceutical composition is present as ^{225}Ac -DOTA-TATE. In some embodiments, after being stored for 144 hours at about 20°C to about 25°C, at least 90 mol% of the ^{225}Ac (i.e., actinium-225) content in the liquid radiopharmaceutical composition (at that time) is present as ^{225}Ac -DOTA-TATE. In some embodiments, after being stored for 168 hours at about 20°C to about 25°C, at least 90 mol% of the ^{225}Ac (i.e., actinium-225) content in the liquid radiopharmaceutical composition (at that time) is present as ^{225}Ac -DOTA-TATE. In some embodiments, after being stored for 192 hours at about 20°C to about 25°C, at least 90 mol% of the ^{225}Ac (i.e., actinium-225) content in the liquid radiopharmaceutical composition (at that time) is present as ^{225}Ac -DOTA-TATE.

[098] In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than a combined amount of about 20 % of free ^{225}Ac and ^{225}Ac present in a fragment of the conjugate (e.g., as ^{225}Ac -DOTA fragment) after 120 hours at about 20°C to 25°C, compared to the total amount of the ^{225}Ac content in the composition. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than a combined amount of about 15 % of free ^{225}Ac and ^{225}Ac present in a fragment of the conjugate (e.g., as ^{225}Ac -DOTA fragment) after 120 hours at about 20°C to 25°C, compared to the total amount of the ^{225}Ac content in the composition. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than a combined amount of about 10 % of free ^{225}Ac and ^{225}Ac present in a fragment of the conjugate (e.g., as ^{225}Ac -DOTA fragment) after 120 hours at about 20°C to 25°C, compared to the total amount of the ^{225}Ac content in the composition. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than a combined amount of about 10 % of free ^{225}Ac and ^{225}Ac present in a fragment of the conjugate (e.g., as ^{225}Ac -DOTA fragment) after 120 hours at about 20°C to 25°C, compared to the total amount of the ^{225}Ac content in the composition. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than a combined amount of about 5 % of free ^{225}Ac

and ^{225}Ac present in a fragment of the conjugate (e.g., as ^{225}Ac -DOTA fragment) after 120 hours at about 20°C to 25°C, compared to the total amount of the ^{225}Ac content in the composition. The total amount of the ^{225}Ac content in a composition can decrease overtime as the radionuclide actinium-225 naturally decays. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than a combined amount of about 10 % of free ^{225}Ac and ^{225}Ac present in a fragment of the conjugate (e.g., as ^{225}Ac -DOTA fragment) after 144 hours at about 20°C to 25°C, compared to the total amount of the ^{225}Ac content in the composition. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than a combined amount of about 10 % of free ^{225}Ac and ^{225}Ac present in a fragment of the conjugate (e.g., as ^{225}Ac -DOTA fragment) after 168 hours at about 20°C to 25°C, compared to the total amount of the ^{225}Ac content in the composition. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than a combined amount of about 10 % of free ^{225}Ac and ^{225}Ac present in a fragment of the conjugate (e.g., as ^{225}Ac -DOTA fragment) after 192 hours at about 20°C to 25°C, compared to the total amount of the ^{225}Ac content in the composition. In some embodiments, the amount of ^{225}Ac is determined by radio-TLC.

[099] In some embodiments, a radiopharmaceutical composition described herein retains at least 90% of the ^{225}Ac (i.e., actinium-225) content in the liquid radiopharmaceutical composition as ^{225}Ac -DOTA-TATE after 120 hours at about 20°C to 25°C as determined by radio-TLC. In some embodiments, a radiopharmaceutical composition described herein retains at least 95% of the ^{225}Ac (i.e., actinium-225) content in the liquid radiopharmaceutical composition as ^{225}Ac -DOTA-TATE after 120 hours at about 20°C to 25°C as determined by radio-TLC. In some embodiments, a radiopharmaceutical composition described herein retains at least 98% of the ^{225}Ac (i.e., actinium-225) content in the liquid radiopharmaceutical composition as ^{225}Ac -DOTA-TATE after 120 hours at about 20°C to 25°C as determined by radio-TLC. In some embodiments, a radiopharmaceutical composition described herein retains at least 99% of the ^{225}Ac (i.e., actinium-225) content in the liquid radiopharmaceutical composition as ^{225}Ac -DOTA-TATE after 120 hours at about 20°C to 25°C as determined by radio-TLC. In some embodiments, a radiopharmaceutical composition described herein retains at least 90% of the ^{225}Ac (i.e., actinium-225) content in the liquid radiopharmaceutical composition as ^{225}Ac -DOTA-TATE after 144 hours at about 20°C to 25°C as determined by radio-TLC. In some embodiments, a radiopharmaceutical composition described herein retains at least 90% of the ^{225}Ac (i.e., actinium-225) content in the liquid radiopharmaceutical composition as ^{225}Ac -DOTA-TATE after 168 hours at about 20°C to 25°C as determined by radio-TLC. In some embodiments, a radiopharmaceutical composition described herein retains at least 90% of the ^{225}Ac (i.e., actinium-

225) content in the liquid radiopharmaceutical composition as ^{225}Ac -DOTA-TATE after 192 hours at about 20°C to 25°C as determined by radio-TLC.

[100] In some embodiments, the liquid radiopharmaceutical compositions comprise a conjugate that comprises actinium-225. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than about 20% free actinium after 168 hours at room temperature, compared to the total amount of the initial chelated actinium content in the composition. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than about 10% free actinium after 168 hours at room temperature, compared to the total amount of the initial chelated actinium content in the composition. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than about 5% free actinium after 168 hours at room temperature, compared to the total amount of the initial chelated actinium content in the composition. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than about 3% free actinium after 168 hours at room temperature, compared to the total amount of the initial chelated actinium content in the composition. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than about 2% free actinium after 168 hours at room temperature, compared to the total amount of the initial chelated actinium content in the composition. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than about 1% free actinium after 168 hours at room temperature, compared to the total amount of the initial chelated actinium content in the composition. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than about a total of 20 mol% of free daughter isotopes of actinium-225 after 168 hours at room temperature, compared to the total amount of the initial chelated actinium content in the composition. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than about a total of 15 mol% of free daughter isotopes of actinium-225 after 168 hours at room temperature, compared to the total amount of the initial chelated actinium content in the composition. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than about a total of 10 mol% of free daughter isotopes of actinium-225 after 168 hours at room temperature, compared to the total amount of the initial chelated actinium content in the composition. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than about a total of 5 mol% of free daughter isotopes of actinium-225 after 168 hours at room temperature, compared to the total amount of the initial chelated actinium content in the composition. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than

about a total of 3 mol% of free daughter isotopes of actinium-225 after 168 hours at room temperature, compared to the total amount of the initial chelated actinium content in the composition. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than about a total of 2 mol% of free daughter isotopes of actinium-225 after 168 hours at room temperature, compared to the total amount of the initial chelated actinium content in the composition. In some embodiments, a radiopharmaceutical composition comprising actinium-225 conjugates contains no more than about a total of 1 mol% of free daughter isotopes of actinium-225 after 168 hours at room temperature, compared to the total amount of the initial chelated actinium content in the composition. In some embodiments, the purity or the molar percentage of the conjugate is determined by radio thin layer chromatography (radio-TLC).

[101] In some embodiments, a radiopharmaceutical composition described herein retains at least 90 % of the ^{225}Ac content bound as part of the conjugate (e.g., as part of ^{225}Ac -DOTA-TATE, ^{225}Ac -DOTA-TOC, ^{225}Ac -HA-DOTA-TATE, or ^{225}Ac -DOTA-JR-11) after 72 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC). In some embodiments, the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content bound as part of the conjugate after 120 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC). In some embodiments, the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content bound as part of the conjugate after 168 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC). In some embodiments, the radiopharmaceutical composition retains at least 95 % of the ^{225}Ac content bound as part of the conjugate after 72 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC). In some embodiments, the radiopharmaceutical composition retains at least 95 % of the ^{225}Ac content bound as part of the conjugate after 120 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC). In some embodiments, the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content bound as part of the conjugate after 120 hours at about 20°C to about 25°C as determined by high performance liquid chromatography/fraction collection (HPLC-FC). In some embodiments, the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content bound as part of the conjugate after 168 hours at about 20°C to about 25°C as determined by high performance liquid chromatography/fraction collection (HPLC-FC). In some embodiments, the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content bound as part of the conjugate after 72 hours at about 20°C to about 25°C as determined by high performance liquid chromatography/fraction collection (HPLC-FC). In some embodiments, the radiopharmaceutical composition retains at least 95 % of the ^{225}Ac content bound as part of the conjugate after 72 hours

at about 20°C to about 25°C as determined by high performance liquid chromatography/fraction collection (HPLC-FC).

Stabilizing agents

[102] In one aspect, disclosed herein are radiopharmaceutical compositions with improved stability. Pharmaceutical compositions described herein can comprise one or more stabilizing agents. In one aspect, provided herein are solutions that comprise one or more stabilizing agents for use in a radiopharmaceutical composition. In some embodiments, the solutions that comprise one or more stabilizing agents are dilution solutions. The one or more stabilizing agents can reduce, prevent, or delay decomposition of the radiopharmaceutical. The decomposition can comprise radiolysis-caused decomposition of the radiopharmaceuticals. The one or more stabilizing agents can reduce, prevent, or delay the decay of radionuclides.

Radiolysis Stabilizer

[103] The one or more stabilizing agents of the herein described pharmaceutical composition can comprise a radiolysis stabilizer. The one or more stabilizing agents can comprise two or more radiolysis stabilizers. The one or more stabilizing agents can comprise a first and a second radiolysis stabilizer. The radiolysis stabilizer can be an amino acid or a peptide or a derivative thereof, a vitamin or a derivative thereof, a lipid or a derivative thereof, a carbohydrate or a derivative thereof, a volume expander or an antioxidant. The radiolysis stabilizer can comprise an amino acid, a peptide or a derivative thereof, a vitamin or a derivative thereof, a lipid or a derivative thereof, a carbohydrate or a derivative thereof, a volume expander, an antioxidant, or a combination thereof. In some embodiments, a radiopharmaceutical composition described herein comprises a means for stabilizing the conjugate comprising a radionuclide. The means for stabilizing the conjugate can be a radiolysis stabilizer described herein. In some embodiments, a radiopharmaceutical composition described herein comprises a means for scavenging free radicals in the composition. In some embodiments, the means for scavenging free radicals in the composition is a radiolysis stabilizer. In some embodiments, a radiopharmaceutical composition described herein comprises a means for reducing a free radical concentration in the composition. In some embodiments, the means for reducing a free radical concentration in the composition is a radiolysis stabilizer. In some embodiments, the reduction of free radicals in the composition reduces radiolysis of the conjugate. In some embodiments, the radiolysis stabilizer is an antioxidant.

[104] The molar ratio of the first and the second radiolysis stabilizer can be from 1:100,000 to 100,000:1, from 1:1,000 to 1,000:1, from 1:100 to 100:1, from 1:20 to 20:1, from 1:10 to 10:1, and from 1:5 to 5:1. The molar ratio of the first and the second radiolysis stabilizer can be from 1:5 to 5:1. The radiolysis stabilizer can be present in the radiopharmaceutical composition at a

concentration of from about 1 μ M, 10 μ M, 0.1mM, 1mM, 5 mM, 10 mM, 25 mM, 50 mM, or 75 mM to about 80 mM, 100 mM, 125 mM, 150 mM, 175 mM, 200 mM, 250 mM, 500 mM, 1 M, 2 M, 3 M, 4 M, 5 M. The radiolysis stabilizer can be present in the radiopharmaceutical composition at a concentration of from about 1 μ M to 5 M. The radiolysis stabilizer can be present in the radiopharmaceutical composition at a concentration of from about 10 μ M to 1 M. The radiolysis stabilizer can be present in the radiopharmaceutical composition at a concentration of from about 0.1 mM to 500 mM. The radiolysis stabilizer can be present in the radiopharmaceutical composition at a concentration of from about 20 mM to 500 mM, about 50 mM to about 500 mM, about 75mM to about 250 mM, or about 250 to about 500 mM. The radiolysis stabilizer can be present in the radiopharmaceutical composition at a concentration of from about 50 mM to 200 mM. The radiolysis stabilizer can be present in the radiopharmaceutical composition at a concentration of from about 75 mM to 150 mM. The radiolysis stabilizer can be present in the radiopharmaceutical composition at a concentration of from about 25 mM to 250 mM. The radiolysis stabilizer can be present in the radiopharmaceutical composition at a concentration of from about 10 mM to 500 mM. The radiolysis stabilizer can be present in the radiopharmaceutical composition at a concentration of from about 20 mM to 100 mM. The radiolysis stabilizer can be present in the radiopharmaceutical composition at a concentration of from about 25 mM to 75 mM. The radiolysis stabilizer can be present in the radiopharmaceutical composition at about 0.001 wt% to about 10 wt%. The radiolysis stabilizer can be present in the radiopharmaceutical composition at about 0.0001 wt% to about 20 wt%, 0.001 wt% to about 10 wt%, 0.01 wt% to about 5 wt%, about 0.05 wt% to about 2 wt%, or about 0.1 wt% to about 1 wt%. The radiolysis stabilizer can be present in the radiopharmaceutical composition at about 0.01 wt% to about 5 wt%. The radiolysis stabilizer can be present in the radiopharmaceutical composition at about 1 wt% to about 10 wt%, about 3 wt% to about 7 wt%, about 4 wt% to about 6 wt%, or about 2 wt% to about 15 wt%. The radiolysis stabilizer can be present in the radiopharmaceutical composition at about 5 wt%. The radiolysis stabilizer can be present in the radiopharmaceutical composition at about 0.05 wt% to about 2 wt%. The radiolysis stabilizer can be present in the radiopharmaceutical composition at about 0.1 wt% to about 1 wt%. The radiolysis stabilizer can also be present in the radiopharmaceutical composition at a concentration of from 0.0001 to 5,000 mg/mL. The radiolysis stabilizer can also be present in the radiopharmaceutical composition at a concentration of from 0.1 to 500 mg/mL. The radiolysis stabilizer can also be present in the radiopharmaceutical composition at a concentration of from 0.01 to 50 mg/mL. The radiolysis stabilizer can also be present in the radiopharmaceutical composition at a concentration of from 0.1 to 5 mg/mL. The radiolysis stabilizer can also be present in the radiopharmaceutical composition at a concentration of from 0.5 to 2 mg/mL. In some embodiments, the radiolysis

stabilizer is dextran (such as Dextran 40). In some embodiments, the radiolysis stabilizer is present in the radiopharmaceutical composition at a concentration of 1 mM to 10 M. In some embodiments, the radiolysis stabilizer is present in the radiopharmaceutical composition at a concentration of 10 mM to 1 M. In some embodiments, the radiolysis stabilizer is present in the radiopharmaceutical composition at a concentration of 20 mM to 500 mM. In some embodiments, the radiolysis stabilizer is present in the radiopharmaceutical composition at a concentration of 40 mM to 250 mM. In some embodiments, the radiolysis stabilizer is present in the radiopharmaceutical composition at a concentration of 20 mM to 300 mM. In some embodiments, the radiolysis stabilizer is present in the radiopharmaceutical composition at a concentration of 80 mM to 125 mM. In some embodiments, the radiolysis stabilizer is present in the radiopharmaceutical composition at a concentration of 90 mM to 110 mM. In some embodiments, the radiolysis stabilizer is present in the radiopharmaceutical composition at a concentration of 100 mM. In some embodiments, the radiolysis stabilizer is ascorbic acid or a salt thereof (such as sodium ascorbate). In some embodiments, the radiolysis stabilizer is ascorbic acid. In some embodiments, the radiolysis stabilizer is sodium ascorbate. In some embodiments, the radiolysis stabilizer is ethanol. In some embodiments, the radiolysis stabilizer is gentisic acid. In some embodiments, the radiolysis stabilizer is a salt of gentisic acid.

[105] The radiolysis stabilizers can comprise an amino acid or a derivative thereof. The radiolysis stabilizers can comprise a peptide or a derivative thereof. The amino acid or a derivative thereof can be a natural amino acid or an unnatural amino acid. The amino acid can act to scavenge chemically active ingredients generated by radiolysis. The amino acid can contain an amino group. The amino acid can comprise optionally an extra reducing heteroatom, such as L-methionine, L-Cysteine, or L-Lysine. The peptide or a derivative thereof can comprise two or more amino acids. The peptide can comprise 2 to 50 amino acids. The peptide can comprise 2 to 30 amino acids. The peptide can comprise 2 to 15 amino acids. The peptide can comprise 2 to 7 amino acids. The peptide can comprise 2 to 4 amino acids. The peptide can comprise 3 amino acids. The amino acid can be an essential amino acid. The amino acid can be a nonessential amino acid. The amino acid can be an aliphatic amino acid. The amino acid can be an aromatic amino acid. The amino acid can be an acidic amino acid. The amino acid can be a basic amino acid. The amino acid can be a hydroxylic amino acid. The amino acid can be a sulfur-containing amino acid. The amino acid can be an amidic amino acid. The amino acid, its derivative, or peptide can be N-Acetyl-L-cysteine, Glutathione, L-Lysine, Selenol-L-methionine, Glutathione, Albumin, Melatonin, Taurine, Alanine, Arginine, Asparagine, Aspartic acid, Cysteine, Glutamine, Glutamic acid, Glycine, Histidine, Isoleucine, Lysine, Methionine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, Valine, and/or derivatives thereof. The amino acid can be a

methionine. The amino acid derivative, such as N-Acetyl-L-cysteine, can have higher solubilities compared to the parent amino acid. The radiolysis stabilizer, such as Thiourea, L-Glutathione, and Lipoic Acid, can comprise an organic sulfur. The organic sulfur can optionally be oxidized to a higher oxidation state and coordinate to free heavy metal ions in a solution.

[106] The radiolysis stabilizers can comprise an antioxidant (or reducing agent or radical scavengers). The radiolysis stabilizers can comprise one or more antioxidants. The antioxidant can comprise a flavonoid or a derivative thereof. The flavonoid can be polyphenol compounds that comprise multiple phenol moieties. A flavonoid can comprise a 15-carbon structure. The 15-carbon structure can further comprise two phenyl rings and a heterocyclic ring. The flavonoid can comprise bioflavonoids, isoflavonoids, or neoflavonoids. The flavonoid can comprise a catechin or a derivative thereof, such as the compounds illustrated in FIG. 1, (2S,3R)-2-(3,4-Dihydroxyphenyl)-3,4-dihydro-1(2H)-benzopyran-3,5,7-triol 3-(3,4,5-trihydroxybenzoate ((-) Catechin gallate or CG), (-)-cis-3,3',4',5,7-Pentahydroxyflavane (Epi-Catechin or EC), 3,4,5-Trihydroxybenzoic acid (Gallic acid), (2R,3R)-5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-3-yl 3,4,5-trihydroxybenzoate (EpiGallo-Catechin gallate or EGCg), (2R,3R)-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol or Epigallo-Catechin (EGC), or (2R,3S)-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol (Gallo-Catechin or GC). The catechins can be administered to a human at a dose from 1mg/kg to 50mg/kg, from 5mg/kg to 40mg/kg, from 10mg/kg to 40mg/kg, from 20mg/kg to 35mg/kg. The flavonoid can comprise (2S,3R)-2-(3,4-Dihydroxyphenyl)-3,4-dihydro-1(2H)-benzopyran-3,5,7-triol 3-(3,4,5-trihydroxybenzoate ((-) Catechin gallate or CG), 3,3',4',5,5',7'-Hexahydroxyflavylium chloride, (-)-cis-3,3',4',5,7-Pentahydroxyflavane (Epi-Catechin or EC), 7-Hydroxy-3-(4'-methoxyphenyl)-4H-benzopyran-4-one, 3,4,5-Trihydroxybenzoic acid (Gallic acid), 3,4',5,7-Tetrahydroxyflavone (Kaempferol), Luteolin, 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxychromen-4-one (Rutin hydrate), Quercetin, (2R,3R)-5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-3-yl 3,4,5-trihydroxybenzoate (EpiGallo-Catechin gallate or EGCg), (2R,3R)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3,4-dihydro-2H-chromen-3-yl] 3,4,5-trihydroxybenzoate, Epi-Catechin Gallate (ECG), (2R,3R)-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol (Epigallo-Catechin or EGC), or (2R,3S)-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol (Gallo-Catechin or GC), or a combination thereof. In some embodiments, the antioxidant is a carotenoid or a derivative thereof. The carotenoid can be a fat-soluble pigment, such as yellow, orange, or red pigments. The carotenoid can be all-trans-Fucoxanthin, Lycopene, Xanthophyll, Beta carotene, Lycopene, or Lutein.

[107] In some embodiment, a herein described pharmaceutical composition comprises an antioxidant that is N-acetyl cysteine, L-Ascorbic acid, N-tert-Butyl- α -phenylnitrone, 3-(3,4-Dihydroxyphenyl)-2-propenoic acid (Caffeic Acid), β -Carotene, Provitamin A, (2S,3R)-2-(3,4-Dihydroxyphenyl)-3,4-dihydro-1(2H)-benzopyran-3,5,7-triol 3-(3,4,5-trihydroxybenzoate ((-) Catechin gallate or CG), 1,4,5-Trihydroxycyclohexanecarboxylic acid, trans-4-Hydroxycinnamic acid (p-Coumaric acid), 3,3',4',5,5',7-Hexahydroxyflavylium chloride, Thiocytic Acid (Dihydrolipoic Acid, DHLA), 4,4',5,5',6,6'-Hexahydroxydiphenic acid 2,6,2',6'-dilactone (Ellagic acid), (-)-cis-3,3',4',5,7-Pentahydroxyflavane (Epi-Catechin or EC), 2-Methoxy-4-(2-propenyl) phenol, trans-4-Hydroxy-3-methoxycinnamic acid (Ferulic acid), 7-Hydroxy-3-(4'-methoxyphenyl)-4H-benzopyran-4-one, all-trans-Fucoanthin, 3,4,5-Trihydroxybenzoic acid (Gallic acid), (2S,3R)-2-(3,4,5-Trihydroxyphenyl)-3,4-dihydro-1(2H)-benzopyran-3,5,7-triol ((-) -Gallocatechin), Glutathione, 2-(3,4-Dihydroxyphenyl)ethanol, 3,4',5,7-Tetrahydroxyflavone (Kaempferol), ($\pm$)-1,2-Dithiolane-3-pentanoic acid, Luteolin, Lycopene, L-Lysine, Neochlorogenic acid, Oleic acid, trans-3,5,4'-Trihydroxystilbene (Resveratrol), 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxychromen-4-one, Rutin hydrate, Selenol-L-methionine, Thiourea, (+)- α -Tocopherol, Xanthophyll, Citric acid (CA), Gentisic acid (GA), Salicylic acid (SA), Erythorbic acid (EA), Phenol, Sodium bisulfite, Butylated hydroxy anisole, Butylated hydroxy toluene, Metabisulfite, Benzyl alcohol, Thymol, Lipoic acid (LA), Thioglycolic acid (TGA), 2,3 Dimercaptopropan-1-ol (BAL), Zinc, Selenium, Albumin, Ethanol, Mannitol, Sucrose, Melatonin, Ebselen, Pyruvic acid, Carboxy-PTIO, Trolox, Ebselen, Uric acid, Edaravone, Beta carotene, NADPH, Lycopene, Lutein, Catalase, Estrogen, Estradiol, Estrinol, Ubiquinol, Copper, Quercetin, Cortisone, Taurine, (2R,3R)-5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-3-yl 3,4,5-trihydroxybenzoate (EpiGallo-Catechin gallate or EGCg), (2R,3R)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3,4-dihydro-2H-chromen-3-yl] 3,4,5-trihydroxybenzoate or Epi-Catechin Gallate (ECG), (2R,3R)-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol (Epigallo-Catechin or EGC), (2R,3S)-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol (Gallo-Catechin or GC), (-)-cis-2-(3,4,5-Trihydroxyphenyl)-3,4-dihydro-1(2H)-benzopyran-3,5,7-triol 3-gallate ((-) -Epigallocatechin-3-O-Gallate), 5-Aminolevulinic Acid hydrate, Ploysorbate 80, Garlic Acid, Sodium L-Ascorbate, Hyaluronic Acid, Dextran 60-90, Selenol, LysaKare, or a combination thereof. Exemplary antioxidants of the present disclosure are further described in **Table 1**.

Table 1. Exemplary Antioxidants

N-Acetyl-L-cysteine	Benzyl alcohol
L-Ascorbic acid	Thymol
N-tert-Butyl- α -phenylnitron	Lipoic acid (LA)
3-(3,4-Dihydroxyphenyl)-2-propenoic acid (Caffeic Acid)	Thioglycolic acid (TGA)
β -Carotene, Provitamin A	2,3 Dimercaptopropan-1-ol (BAL)
(2S,3R)-2-(3,4-Dihydroxyphenyl)-3,4-dihydro-1(2H)-benzopyran-3,5,7-triol 3-(3,4,5-trihydroxybenzoate ((-) Catechin gallate) (from green tea)	Zinc
1,4,5-Trihydroxycyclohexanecarboxylic acid	Selenium
trans-4-Hydroxycinnamic acid (p-Coumaric acid)	Albumin
3,3',4',5,5',7-Hexahydroxyflavylium chloride	Ethanol
Thiocytic Acid (Dihydrolipoic Acid, DHLA)	Mannitol
4,4',5,5',6,6'-Hexahydroxydiphenic acid 2,6,2',6'-dilactone (Ellagic acid)	Sucrose
(-)-cis-3,3',4',5,7-Pentahydroxyflavane (from green tea)	Melatonin
2-Methoxy-4-(2-propenyl) phenol	Ebselen
trans-4-Hydroxy-3-methoxycinnamic acid (Ferulic acid)	Pyruvic acid
7-Hydroxy-3-(4'-methoxyphenyl)-4H-benzopyran-4-one	2-(4-Carboxyphenyl)-4,5-dihydro-4,4,5,5-tetramethyl-1H-imidazol-1-yloxy-3-oxide potassium salt, 2-(4-Carboxyphenyl)-4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxide (Carboxy-PTIO) Salt
all-trans-Fucoanthin	Trolox
3,4,5-Trihydroxybenzoic acid (Gallic acid)	Ebselen
(2S,3R)-2-(3,4,5-Trihydroxyphenyl)-3,4-dihydro-1(2H)-benzopyran-3,5,7-triol ((-)-Gallocatechin)(from green tea)	Uric acid
Glutathione	Edaravone
2-(3,4-Dihydroxyphenyl)ethanol	Beta carotene
3,4',5,7-Tetrahydroxyflavone (Kaempferol)	Nicotinamide adenine dinucleotide phosphate (NADPH)
($\pm$)-1,2-Dithiolane-3-pentanoic acid	Lycopene
Luteolin	Lutein
Lycopene (from tomato)	Catalase
Neochlorogenic acid	Estrogen

Oleic acid	Estradiol
trans-3,5,4'-Trihydroxystilbene (Resveratrol)	Estriol
2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3- [(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6- [[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2- yl]oxymethyl]oxan-2-yl]oxychromen-4- one;hydrateRutin hydrate	Ubiquinol
L-methionine	Copper
Thiourea	Quercetin
(+)- α -Tocopherol	Cortisone
Xanthophyll	2,3-dimercaptosuccinic acid (DMSA) or monisoamyl derivative (MiADMSA)
Natural L-amino acids: Alanine, Arginine, Asparagine, Aspartic acid, Cysteine, Glutamine, Glutamic acid, Glycine, Histidine, Isoleucine, Lysine, Methionine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, Valine, and their derivatives	Taurine
Citric acid (CA)	Dextran 40
Gentisic acid (GA)	Dextran 70
Salicylic acid (SA)	PEG 3350
Erythorbic acid (EA)	PEG 4000
Phenol	Polygeline
Sodium bisulfite	Gelofusine
Butylated hydroxy anisole	PLENVU (polyethylene glycol 3350, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride)
Butylated hydroxy toluene	Cyclodextrins
Glutathione	Metabisulfite
PEG 400	PEG 1000
PEG (e.g., PEG having a number average molecular weight of about 200-8000)	(-)-Epigallocatechin-3-O-Gallate
5-Aminolevulinic Acid hydrate	Ploysorbate 80
Garlic Acid	Sodium L-Ascorbate
Hyaluronic Acid	Dextran 60-90
Selenol	LysaKare

[108] In some embodiments, the radiolysis stabilizers comprise a salt, an ester, an amide, an enantiomer, or an acetylation derivative of a compound of Table 1, or a combination thereof. In some embodiments, the radiolysis stabilizer functions as a pH stabilizer.

[109] The radiolysis stabilizers can comprise a vitamin or a derivative thereof. The radiolysis stabilizers can comprise one or more vitamins or derivatives thereof. In some embodiments, the vitamin or a derivative thereof is L-Ascorbic acid, β -Carotene, Provitamin A, (+)- α -Tocopherol, Erythorbic acid (EA), Trolox, or Lutein. In some embodiments, the radiolysis stabilizer is ascorbic acid or a salt thereof (such as sodium ascorbate). In some embodiments, the radiolysis stabilizer is ascorbic acid. In some embodiments, the radiolysis stabilizer is sodium ascorbate. In some embodiments, the radiolysis stabilizer is ethanol. In some embodiments, the radiolysis stabilizer is gentisic acid. In some embodiments, the radiolysis stabilizer is a salt of gentisic acid.

[110] In some embodiments, the radiolysis stabilizer comprises ascorbic acid or a salt thereof. In some embodiments, the radiolysis stabilizer comprises sodium L-ascorbate. In some embodiments, the radiolysis stabilizer comprises sodium ascorbate (e.g., sodium L-ascorbate) and is present in the radiopharmaceutical composition at a concentration of 1 mM to 10 M. In some embodiments, the radiolysis stabilizer comprises sodium L-ascorbate and is present in the radiopharmaceutical composition at a concentration of 10 mM to 1 M. In some embodiments, the radiolysis stabilizer comprises sodium L-ascorbate and is present in the radiopharmaceutical composition at a concentration of 20 mM to 500 mM. In some embodiments, the radiolysis stabilizer comprises sodium L-ascorbate and is present in the radiopharmaceutical composition at a concentration of 40 mM to 250 mM. In some embodiments, the radiolysis stabilizer comprises sodium L-ascorbate and is present in the radiopharmaceutical composition at a concentration of 80 mM to 125 mM. In some embodiments, the radiolysis stabilizer comprises sodium L-ascorbate and is present in the radiopharmaceutical composition at a concentration of 90 mM to 110 mM. In some embodiments, the radiolysis stabilizer comprises sodium L-ascorbate and is present in the radiopharmaceutical composition at a concentration of 100 mM. In some embodiments, the radiolysis stabilizer comprises ascorbic acid or a salt thereof. In some embodiments, the radiolysis stabilizer comprises ascorbic acid or a salt thereof (e.g., sodium L-ascorbate) and is present in the radiopharmaceutical composition at a concentration of 1 mM to 10 M. In some embodiments, the radiolysis stabilizer comprises ascorbic acid or a salt thereof and is present in the radiopharmaceutical composition at a concentration of 10 mM to 1 M. In some embodiments, the radiolysis stabilizer comprises ascorbic acid or a salt thereof and is present in the radiopharmaceutical composition at a concentration of 20 mM to 500 mM. In some embodiments, the radiolysis stabilizer comprises ascorbic acid or a salt thereof and is present in the radiopharmaceutical composition at a concentration of 40 mM to 250 mM. In some embodiments,

the radiolysis stabilizer comprises ascorbic acid or a salt thereof and is present in the radiopharmaceutical composition at a concentration of 20 mM to 300 mM. In some embodiments, the radiolysis stabilizer comprises ascorbic acid or a salt thereof and is present in the radiopharmaceutical composition at a concentration of 80 mM to 125 mM. In some embodiments, the radiolysis stabilizer comprises ascorbic acid or a salt thereof and is present in the radiopharmaceutical composition at a concentration of 90 mM to 110 mM. In some embodiments, the radiolysis stabilizer comprises ascorbic acid or a salt thereof and is present in the radiopharmaceutical composition at a concentration of 100 mM.

[111] In some embodiments, an ascorbic acid or a salt thereof (such as sodium ascorbate) is present in the radiopharmaceutical composition at a concentration of 1 mM to 10 M. In some embodiments, the sodium ascorbate is present in the radiopharmaceutical composition at a concentration of 10 mM to 1 M. In some embodiments, the sodium ascorbate is present in the radiopharmaceutical composition at a concentration of 20 mM to 500 mM. In some embodiments, the sodium ascorbate is present in the radiopharmaceutical composition at a concentration of 40 mM to 250 mM. In some embodiments, the sodium ascorbate is present in the radiopharmaceutical composition at a concentration of 80 mM to 125 mM. In some embodiments, the sodium ascorbate is present in the radiopharmaceutical composition at a concentration of 90 mM to 110 mM. In some embodiments, the sodium ascorbate is present in the radiopharmaceutical composition at a concentration of about 100 mM. In some embodiments, the sodium ascorbate is present in the radiopharmaceutical composition at a concentration of about 1 mg/mL to 100 mg/mL. In some embodiments, the sodium ascorbate is present in the radiopharmaceutical composition at a concentration of about 5 mg/mL to 50 mg/mL. In some embodiments, the sodium ascorbate is present in the radiopharmaceutical composition at a concentration of about 10 mg/mL to 30 mg/mL. In some embodiments, the sodium ascorbate is present in the radiopharmaceutical composition at a concentration of 18.5 ± 4.63 mg/mL. In some embodiments, the sodium ascorbate is present in the radiopharmaceutical composition at a concentration of 18.5 ± 5 mg/mL. In some embodiments, the sodium ascorbate is present in the radiopharmaceutical composition at a concentration of 18.5 ± 10 mg/mL. In some embodiments, the sodium ascorbate is present in the radiopharmaceutical composition at a concentration of about 18.5 mg/mL. In some embodiments, the sodium ascorbate is sodium L-ascorbate.

[112] The radiolysis stabilizers can comprise a fatty acid or a derivative thereof. The radiolysis stabilizers can comprise one or more lipids. The lipids can be fatty acids or derivatives thereof. In some embodiments, the fatty acid is a saturated fatty acid. In some embodiments, the fatty acid is an unsaturated fatty acid. The fatty acid can comprise a mono-unsaturated fatty acid. The fatty acid can comprise a poly-unsaturated fatty acid. The fatty acid can comprise a trans-fat. The fatty

acid can comprise a C₃ to C₄₀ fatty acid, C₆ to C₃₀ fatty acid, C₆ to C₂₀ fatty acid, and C₆ to C₁₀ fatty acid. In some embodiments, the fatty acid is a C₆ to C₃₀ fatty acid. The fatty acid can comprise a saturated or unsaturated C₆ to C₃₀ fatty acid. The fatty acid can comprise a saturated or unsaturated C₁₉ to C₂₀ fatty acid. The fatty acid can comprise a saturated or unsaturated C₁₂ to C₂₆ fatty acid. In some embodiments, the fatty acid comprises oleic acid, Myristoleic acid, Palmitoleic acid, Sapienic acid, Elaidic acid, Vaccenic acid, or Linoleic acid, α -Linolenic acid, or a combination thereof.

[113] In some embodiments, the radiolysis stabilizers comprise a lipid that is a steroid or a derivative thereof. In some embodiments, the steroid can be a corticosteroid, such as Estrogen, Estradiol, Estrinol, or Cortisone. The steroid can have four carbon rings. In some embodiments, the steroid can be Estrogen, Estradiol, Estrinol, or Cortisone.

[114] The radiolysis stabilizers can comprise a volume expander. In some embodiments, the volume expander is present in the radiopharmaceutical composition at a concentration of from about 0.001 wt% to 80% wt%. In some embodiments, the volume expander can expand the volume of a liquid, such as human blood volume. The volume expander can serve as an absorptive radio-protectant. The volume expander can mimic human serum albumin. The volume expander can comprise human albumin. The volume expander can comprise polymers, such as polyethylene glycol (PEG), a glucose polymer, or polymer mixtures. A glucose polymer can be a Dextran or a saccharide, such as an oligosaccharide. The glucose polymer can have a number average molecular weight from 1kDa to 40,000,000kDa, from 5kDa to 1,000,000kDa, from 10kDa to 500,000kDa, from 15kDa to 1,000kDa, from 20kDa to 100kDa, or from 30kDa to 50kDa. The glucose polymer can have an average molecular of about 20-60 kDa, e.g., about 40kDa. The glucose polymer can be linear or cyclic. The cyclic form glucose polymer can be cyclic oligosaccharides, such as cyclodextrins. The cyclodextrins can comprise a macrocyclic ring of glucose subunits joined by α -1,4 glycosidic bonds. The macrocyclic ring can comprise 6 to 8 glucose subunits, such as, α (alpha)-cyclodextrin, β (beta)-cyclodextrin, and γ (gamma)-cyclodextrin. The polymer mixture, such as an artificial colloid, can comprise the glucose polymer from 0.001 wt% to 80% wt%. The polymer mixture can comprise the glucose polymer from 0.1 wt% to 50% wt%. The polymer mixture can comprise the glucose polymer from 1 wt% to 20% wt%. The polymer mixture can be a mixture comprise the glucose polymer from 5 wt% to 15% wt%. The polymer mixture can comprise from 0.1%wt to 15%wt glucose polymer, or from 1%wt to 10% glucose polymer. The Dextran can be Dextran 40 and Dextran 70. The Dextran can have a number average molecular weight of about 5 to 100 kDa. The Dextran can have a number average molecular weight of about 40 to 70 kDa. The Dextran can have a number average molecular weight of 40, 60, or 70 kDa. Dextran 40 can be provided as a Dextran 40 mixture, such

as a 10% Dextran 40 solution in 0.9% sodium chloride in an infusion bag. The Dextran 40 mixture can comprise from 0.1%wt to 15%wt Dextran 40, or from 1%wt to 10% Dextran 40. The Dextran 40 mixture can have a total osmolality from 300 mOsmol/L to 450 mOsmol/L. The Dextran 40 mixture can have a total osmolality from 350 mOsmol/L to 420 mOsmol/L. The Dextran 40 mixture can have a total osmolality from 380 mOsmol/L to 400 mOsmol/L. The Dextran 40 mixture can have a total osmolality of 390 mOsmol/L. The polymer can be a Polyethylene glycol (PEG), such as PEG 4000, PEG 3350. In some embodiments, the PEG has a number average molecular weight of about 200 to 20,000, 1000 to 10,000, 2000 to 8000, 3000 to about 5000, or 3000 to 4000. The polymer mixture can comprise PEG, such as PLENVU, a combination of PEG 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride. The polymer can be a gelatin or a modified gelatin, such as polygeline and succinylated gelatin. The polygeline can have a number average molecular weight from 5kDa to 50kDa, from 10kDa to 45kDa, from 20kDa to 50kDa, from 30kDa to 40kDa. The polygeline can have an average molecular of 35kDa. The polymer mixture can be a mixture containing polygeline. A mixture comprising polygeline, such as Haemaccel, can also contain calcium chloride, potassium chloride and/or sodium chloride. The polymer mixture can comprise modified fluid gelatin, such as succinylated gelatin. The polymer mixture can be a solution, such as Gelofusine. Gelofusine can comprise 4%w/v succinylated gelatin.

[115] The radiolysis stabilizers can comprise a carbohydrate or a derivative thereof. The carbohydrate can be a saccharide. The saccharide can be a monosaccharide. The saccharide can be a disaccharide, an oligosaccharide, or a polysaccharide. Exemplary disaccharides include a mannitol and a sucrose. The polysaccharide can be a Dextran such as Dextran 40 and Dextran 70. The Dextran can have a molecular weight of about 10-200, 20-100, 30-50, or 40-70 kDa. The polysaccharide can have a number average molecular weight from 5kDa to 1,000,000kDa, from 10kDa to 500,000kDa, from 15kDa to 1,000kDa, from 20kDa to 100kDa, or from 30kDa to 80kDa. The oligosaccharide can be a cyclic oligosaccharide, such as cyclodextrin. The cyclodextrin can comprise a macrocyclic ring of glucose subunits joined by α -1,4 glycosidic bonds. The macrocyclic ring can comprise 6 to 8 glucose subunits, such as, α (alpha)-cyclodextrin, β (beta)-cyclodextrin, and γ (gamma)-cyclodextrin. The polysaccharide can be a Dextran. The carbohydrate can be Mannitol, Sucrose, Dextran (e.g., Dextran 40, Dextran 70), or Cyclodextrins (α -cyclodextrin, β -cyclodextrin, or γ -cyclodextrin), such as 2-Hydroxypropyl- β -cyclodextrin (HP- β -CD) or sulfobutylether- β -Cyclodextrin (SEB- β -CD).

Free metal chelator

[116] The one or more stabilizing agents can comprise a free metal chelator. In some embodiments, a radiopharmaceutical composition disclosed herein comprises one or more free

metal chelators. In some embodiments, a radiopharmaceutical composition described herein comprises a means for scavenging free radionuclide in the radiopharmaceutical composition. The means for scavenging free radionuclide in the radiopharmaceutical composition can be a free metal chelator described herein. In some embodiments, a radiopharmaceutical composition described herein comprises a means for scavenging free radionuclide in the radiopharmaceutical composition and maintaining a low level of free radionuclide (such as free Ac-225). In some embodiments, the level of free radionuclide (such as free Ac-225) in the composition is maintained below about 0.05 mCi/L. In some embodiments, a radiopharmaceutical composition disclosed herein comprises a free metal chelator configured to maintain a low level of free radionuclide in the composition. In some embodiments, the level of free radionuclide in the composition is maintained below about 0.01 mCi/L. In some embodiments, the level of free radionuclide in the composition is maintained below about 1 mCi/L. In some embodiments, the level of free radionuclide in the composition is maintained below about 0.5 mCi/L. In some embodiments, the level of free radionuclide in the composition is maintained below about 0.001 mCi/L. In some embodiments, the level of free radionuclide in the composition is maintained below about 0.02 mCi/L. In some embodiments, the level of free radionuclide is maintained for a period of time such as 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, or 168 hours. In some embodiments, the level of free radionuclide is maintained for a period of 72 hours. In some embodiments, the level of free radionuclide is maintained for a period of 120 hours. In some embodiments, the level of free radionuclide is maintained at a temperature of about 20°C to about 25°C.

[117] In some embodiments, a radiopharmaceutical composition disclosed herein comprises one or more free metal chelators. The one or more stabilizing agents can comprise two or more free metal chelators. In some embodiments, the free metal chelator is not attached to the targeting ligand. The one or more stabilizing agents can comprise a first and a second free metal chelator. In some embodiments, the molar ratio of the first and the second free metal chelator is from 1:100,000 to 100,000:1, from 1:1,000 to 1,000:1, from 1:100 to 100:1, from 1:20 to 20:1, from 1:10 to 10:1, and from 1:5 to 5:1. In some embodiments, the molar ratio of the first and the second free metal chelator is from 1:5 to 5:1. The free metal chelator can be present in the radiopharmaceutical composition at about 0.001 wt% to about 10 wt%. The free metal chelator can be present in the radiopharmaceutical composition at about 0.0001 wt% to about 20 wt%, 0.001 wt% to about 10 wt%, 0.01 wt% to about 5 wt%, about 0.05 wt% to about 2 wt%, or about 0.1 wt% to about 1 wt%. The free metal chelator can be present in the radiopharmaceutical composition at about 0.01 wt% to about 5 wt%. The free metal chelator can be present in the radiopharmaceutical composition at about 0.05 wt% to about 2 wt%. The free metal chelator can be present in the radiopharmaceutical composition at about 0.1 wt% to about 1 wt%. The free metal chelator can

also be present in the radiopharmaceutical composition at a concentration of from 0.0001 to 5,000 mg/mL. The free metal chelator can also be present in the radiopharmaceutical composition at a concentration of from 0.1 to 500 mg/mL. The free metal chelator can also be present in the radiopharmaceutical composition at a concentration of from 0.01 to 50 mg/mL. The free metal chelator can also be present in the radiopharmaceutical composition at a concentration of from 0.1 to 5 mg/mL. The free metal chelator can also be present in the radiopharmaceutical composition at a concentration of from 0.5 to 2 mg/mL. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at a concentration of from 0.01 mg/mL to 2 mg/mL. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at a concentration of from 0.01 mg/mL to 5 mg/mL. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at a concentration of from 0.001 mg/mL to 10 mg/mL. In some embodiments, the free metal chelator is selected from Table 2.

[118] The free metal chelator can be a linear or cyclic. The linear free metal chelator, such as Ethylenediaminetetraacetic acid (EDTA) and Diethylenetriaminepentaacetic acid (DTPA), can be a heavy metal poisoning antidote or a free heavy metal scavenger. The DTPA can be present in the radiopharmaceutical composition at a concentration from 0.001 mg/mL to 2.5 mg/mL, from 0.01 mg/mL to 5mg/mL, from 0.02 mg/mL to 3mg/mL, from 0.04mg/mL to 1 mg/mL, or from 0.05 mg/mL to 0.1 mg/mL. In some embodiments, the free metal chelator (such as DTPA) is present in the radiopharmaceutical composition at a concentration of about 0.05 mg/mL. In some embodiments, the free metal chelator (such as DTPA) is present in the radiopharmaceutical composition at a concentration of about 0.01 to 0.1 mg/mL. In some embodiments, the free metal chelator (such as DTPA) is present in the radiopharmaceutical composition at a concentration of about 0.02 to 0.07 mg/mL. In some embodiments, the free metal chelator is DTPA and is present in the radiopharmaceutical composition at a concentration from 0.001 mg/mL to 10 mg/mL. In some embodiments, the free metal chelator is DTPA and is present in the radiopharmaceutical composition at a concentration from 0.01mg/mL to 10 mg/mL. In some embodiments, the free metal chelator is DTPA and is present in the radiopharmaceutical composition at a concentration from 0.01mg/mL to 5mg/mL. In some embodiments, the free metal chelator is DTPA and is present in the radiopharmaceutical composition at a concentration from 0.02mg/mL to 2.5mg/mL. In some embodiments, the free metal chelator is DTPA and is present in the radiopharmaceutical composition at a concentration from 0.04mg/mL to 1mg/mL. In some embodiments, the free metal chelator is DTPA and is present in the radiopharmaceutical composition at a concentration from 0.01 to 0.25 mg/mL. In some embodiments, the free metal chelator is DTPA and is present in the radiopharmaceutical composition at a concentration from 0.02 to 0.125 mg/mL. In some embodiments, the free metal chelator is DTPA and is present in the radiopharmaceutical

composition at a concentration from 0.04 to 0.06 mg/mL. In some embodiments, the free metal chelator is DTPA and is present in the radiopharmaceutical composition at a concentration of 0.05 mg/mL. In some embodiments, the free metal chelator is DTPA and is present in the radiopharmaceutical composition at a concentration of 0.05 mg/mL to 2 mg/mL. In some embodiments, the free metal chelator is DTPA and is present in the radiopharmaceutical composition at a concentration of 0.01 mg/mL to 0.5 mg/mL. In some embodiments, the free metal chelator is DTPA and is present in the radiopharmaceutical composition at a concentration of 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.6, 0.7, 0.8, 0.9 or 1.0 mg/mL.

[119] In some embodiments, a radiopharmaceutical composition disclosed herein comprises one or more free metal chelators. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at a concentration of about 0.05 mg/mL. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at a concentration of about 0.01 to 0.1 mg/mL. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at a concentration of about 0.01 to 2 mg/mL. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at a concentration of about 0.01 to 3 mg/mL. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at a concentration of about 0.01 to 4 mg/mL. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at a concentration of about 0.01 to 5 mg/mL. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at a concentration of about 0.02 to 0.07 mg/mL. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at a concentration from 0.01mg/mL to 10 mg/mL. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at a concentration from 0.01mg/mL to 5mg/mL. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at a concentration from 0.001 mg/mL to 10 mg/mL. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at a concentration from 0.02mg/mL to 2.5mg/mL. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at a concentration from 0.04mg/mL to 1mg/mL. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at a concentration from 0.01 to 0.25 mg/mL. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at a concentration from 0.02 to 0.125 mg/mL. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at a concentration from 0.04 to 0.06 mg/mL. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at a concentration of 0.05 mg/mL to 2 mg/mL. In some embodiments, the free metal

chelator is present in the radiopharmaceutical composition at a concentration of 0.01 mg/mL to 0.5 mg/mL. In some embodiments, the free metal chelator is present in the radiopharmaceutical composition at a concentration of 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.6, 0.7, 0.8, 0.9 or 1.0 mg/mL. The free metal chelator can also prevent potential hepatotoxicity caused by free radioactive metal ion when administered into a subject, such as a human subject. The cyclic free metal chelator can be a macrocyclic free metal chelator, such as 1,4,7-Triazacyclononane-1,4,7-triacetic acid (NOTA) 2,2',2'',2'''-(1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetrayl)tetraacetic acid (DOTA). The macrocyclic free metal chelator can have strong chelation ability and used in lower concentration. The free metal chelator can comprise Ethylenediaminetetraacetic acid (EDTA), Diethylenetriaminepentaacetic acid (DTPA), 2-S-(4-Isothiocyanatobenzyl)-1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA), Triethylenetetramine (TETA), 1, 4, 7, 10, 13-pentaazacyclopentadecane-N, N', N'', N''', N''''-pentaacetic acid (PEPA), TETPA, 2,2',2''-(10-(2,6-dioxotetrahydro-2H-pyran-3-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (DOTA-GA), 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic acid (DOTP), Deferoxamine (DFO), N, N-bis(2-hydroxybenzyl)ethylenediamine-N,N-diacetic acid (HBED), 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic acid) (DOTP), 6,6'-((1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))dipicolinic acid (Macropa), Meso-2,3-dimercaptosuccinic acid (DMSA), Dimercaptopropane sulfonate (DMPS), Dihydrolipoic acid (DHLA), Lipoic acid (LA), Thioglycolic acid (TGA), 2,3 Dimercaptopropan-1-ol (BAL), or a combination thereof. The free metal chelator can comprise EDTA, DTPA, or Macropa. In some embodiments, the free metal chelator is EDTA. In some embodiments, the free metal chelator is DTPA. In some embodiments, the free metal chelator is Macropa. In some embodiments, the free metal chelator is TETA. In some embodiments, the free metal chelator is PEPA. In some embodiments, the free metal chelator is TETPA. In some embodiments, the free metal chelator comprises one or more compounds selected from Table 2. In some embodiments, the free metal chelator comprises 2 compounds selected from Table 2, or salts thereof. In some embodiments, the free metal chelator comprises 3 compounds selected from Table 2, or salts thereof. Exemplary free metal chelators of the present disclosure are further described in **Table 2**.

Table 2. Exemplary Free Metal Chelators

Ethylenediaminetetraacetic acid (EDTA)	N, N-bis(2-hydroxybenzyl)ethylenediamine-N, N-diacetic acid (HBED)
Diethylenetriaminepentaacetic acid (DTPA)	1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic acid) (DOTP)

1,4,7-Triazacyclononane-1,4,7-triacetic acid (NOTA)	6,6'-((1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))dipicolinic acid (Macropa)
2,2',2'',2'''-(1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetrayl)tetraacetic acid (DOTA)	Meso-2,3-dimercaptosuccinic acid (DMSA)
Triethylenetetramine (TETA)	Dimercaptopropane sulfonate (DMPS)
1, 4, 7, 10, 13-pentaazacyclopentadecane-N, N', N'', N''', N''''-pentaacetic acid (PEPA)	Dihydrolipoic acid (DHLA)
triethylenetetraminepentaacetic acid (TETPA)	Lipoic acid (LA)
2,2',2''-(10-(2,6-dioxotetrahydro-2H-pyran-3-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triaticetic acid (DOTA-GA)	Thioglycolic acid (TGA)
1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic acid (DOTP)	2,3 Dimercaptopropan-1-ol (BAL)
Deferoxamine (DFO)	

pH Stabilizer

[120] In some embodiments, a radiopharmaceutical composition disclosed herein comprises one or more pH stabilizers. In some embodiments, a radiopharmaceutical composition described herein comprises a means for maintaining a pH of the radiopharmaceutical composition. The means for maintaining a pH of the radiopharmaceutical composition can be a pH stabilizer described herein. In some embodiments, a radiopharmaceutical composition described herein comprises a means for maintaining a pH in the radiopharmaceutical composition at about 4-8. In some embodiments, a radiopharmaceutical composition described herein comprises a means for maintaining a pH in the radiopharmaceutical composition at about 5-7. In some embodiments, a radiopharmaceutical composition described herein comprises a means for maintaining a pH in the radiopharmaceutical composition at about 6-8. In some embodiments, a radiopharmaceutical composition described herein comprises a means for maintaining a pH in the radiopharmaceutical composition at about 5.5-6.5. In some embodiments, a radiopharmaceutical composition described herein comprises a means for maintaining a pH in the radiopharmaceutical composition at about 4-7. In some embodiments, a radiopharmaceutical composition disclosed herein comprises a pH stabilizer configured to maintain a pH in the composition. In some embodiments, a radiopharmaceutical composition disclosed herein comprises a pH stabilizer configured to maintain a pH of 4-8 in the composition. In some embodiments, a radiopharmaceutical composition disclosed herein comprises a pH stabilizer configured to maintain a pH of 5-7 in the

composition. In some embodiments, a radiopharmaceutical composition disclosed herein comprises a pH stabilizer configured to maintain a pH of 6-8 in the composition. In some embodiments, a radiopharmaceutical composition disclosed herein comprises a pH stabilizer configured to maintain a pH of 5.5-6.5 in the composition. In some embodiments, a radiopharmaceutical composition disclosed herein comprises a pH stabilizer configured to maintain a pH of 4-7 in the composition.

[121] In some embodiments, stabilities of the described radiopharmaceutical compositions can vary at different pH values. When pH falls out of certain range, leakage of the radioactive metal may also affect radiochemical purity of the formulated dose and shorten its shelf-life. Accordingly, in some embodiments, the one or more stabilizing agents can comprise pH stabilizing buffers in addition to the radiolysis protectants and/or free metal chelating agents. In some embodiments, a radiopharmaceutical composition disclosed herein comprises one or more pH stabilizers. Exemplary pH stabilizers include sodium acetate/acetic acid and sodium L-ascorbate/L-ascorbic acid aqueous buffers.

[122] The one or more stabilizing agents can comprise one or more pH stabilizers. The one or more pH stabilizers can function as a pH buffer. The one or more pH stabilizers can function as a pH buffer. The one or more pH stabilizers can comprise an organic acid. The organic acid can comprise an acetic acid, fumaric acid, ascorbic acid, propionic acid, benzene sulfonic acid, carbonic acid, citrate acid, aspartic acid, maleic acid, methane sulfonic acid, or tartaric acid. The one or more pH stabilizers can comprise an inorganic acid. In some embodiments, the inorganic acid is hydrobromic acid, hydrochloric acid, phosphoric acid, boric acid, sulfuric acid, or a combination thereof. The one or more pH stabilizers can comprise a base. The base can comprise tromethamine (Tris), ammonium hydroxide, diethanolamine, sodium hydroxide, or a combination thereof. The one or more pH stabilizers can comprise an amino acid or a salt thereof. The one or more pH stabilizers can comprise glycine, lysine, arginine, histidine, or a salt thereof. The one or more pH stabilizers can comprise an alkaline salt. The alkaline salt can comprise sodium acetate, sodium ascorbate, sodium benzoate, sodium bicarbonate, sodium carbonate, tribasic sodium phosphate acid, dibasic sodium phosphate acid, monobasic sodium phosphate acid, sodium tartrate, sodium lactate, sodium succinate, or disodium succinate, or a combination thereof. The sodium ascorbate can be present in the radiopharmaceutical composition at a concentration of from about 50 mM to 200 mM. The one or more pH stabilizers can comprise an acid salt. The acid salt can be ammonium sulfate. The one or more pH stabilizers can comprise Sodium acetate, Sodium ascorbate, Ascorbic acid, Acetic 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, 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, tromethamine (tris), or a combination thereof. Exemplary pH stabilizers of the present disclosure are further described in **Table 3**.

Table 3. Exemplary pH Stabilizers

Sodium acetate	Citrate acid
Acetic acid	Hydrobromic acid
Sodium L-ascorbate	Glycine
L-Ascorbic acid	Histidine
Fumaric acid	Sodium lactate
Propionic acid	(L)-Lysine
Ammonium sulfate	Maleic acid
Ammonium hydroxide	Methane sulfonic acid
Arginine	Phosphate acid
Aspartic acid	Monobasic sodium phosphate acid
Benzene sulfonic acid	Tribasic sodium phosphate acid
Sodium benzoate	Dibasic sodium phosphate acid
Sodium bicarbonate	Sodium hydroxide
Boric acid	Sodium/disodium succinate
Sodium carbonate,	Sulfuric acid
Carbon dioxide	Sodium tartrate
Diethanolamine	Tartaric acid
Tromethamine (Tris)	

[123] In some embodiments, the pH stabilizers can reduce the pH changes and maintain the radiopharmaceutical purity, which reduces the decomposition of the conjugate and thereby extending the shelf-life of the radiopharmaceutical compositions described herein. The one or more stabilizing agents can comprise a pH stabilizer. The one or more stabilizing agents can comprise two or more pH stabilizers. The one or more stabilizing agents can comprise a first and a second pH stabilizer. In some embodiments, the molar ratio of the first and the second pH stabilizer is from 1: 100,000 to 100,000:1, from 1:1,000 to 1,000:1, from 1:100 to 100:1, from 1:20 to 20:1, from 1:10 to 10:1, and from 1:5 to 5:1. In some embodiments, the molar ratio of the first and the second pH stabilizer is from 1:5 to 5:1. The pH stabilizer can be present in the radiopharmaceutical composition at about 0.001 wt% to about 10 wt%. The pH stabilizer can be present in the radiopharmaceutical composition at about 0.0001 wt% to about 20 wt%, 0.001 wt% to about 10 wt%, 0.01 wt% to about 5 wt%, about 0.05 wt% to about 2 wt%, or about 0.1 wt% to

about 1 wt%. The pH stabilizer can be present in the radiopharmaceutical composition at about 0.01 wt% to about 5 wt%. The pH stabilizer can be present in the radiopharmaceutical composition at about 0.05 wt% to about 2 wt%. The pH stabilizer can be present in the radiopharmaceutical composition at about 0.1 wt% to about 1 wt%. The pH stabilizer can also be present in the radiopharmaceutical composition at a concentration of from about 1 μ M, 10 μ M, 0.1mM, 1mM, 5 mM, 10 mM, 25 mM, 50 mM, or 75 mM to about 80 mM, 100 mM, 125 mM, 150 mM, 175 mM, 200 mM, 250 mM, 500 mM, 1 M, 2 M, 3 M, 4 M, or 5 M. The pH stabilizer can be present in the radiopharmaceutical composition at a concentration of from about 1 μ M to 5 M. The pH stabilizer can be present in the radiopharmaceutical composition at a concentration of from about 10 μ M to 1 M. The pH stabilizer can be present in the radiopharmaceutical composition at a concentration of from about 0.1 mM to 500 mM. The pH stabilizer can be present in the radiopharmaceutical composition at a concentration of from about 10 mM to 500 mM. The pH stabilizer can be present in the radiopharmaceutical composition at a concentration of from about 50 mM to 250 mM. The pH stabilizer can be present in the radiopharmaceutical composition at a concentration of from about 25 mM to 350 mM. The pH stabilizer can be present in the radiopharmaceutical composition at a concentration of from about 80 mM to 200 mM. The pH stabilizer can be present in the radiopharmaceutical composition at a concentration of from about 80 mM to 120 mM. The pH stabilizer can also be present in the radiopharmaceutical composition at a concentration of from 0.0001 to 5,000 mg/mL. The pH stabilizer can also be present in the radiopharmaceutical composition at a concentration of from 0.1 to 500 mg/mL. The pH stabilizer can also be present in the radiopharmaceutical composition at a concentration of from 0.01 to 50 mg/mL. The pH stabilizer can also be present in the radiopharmaceutical composition at a concentration of from 0.1 to 5 mg/mL. The pH stabilizer can also be present in the radiopharmaceutical composition at a concentration of from 0.5 to 2 mg/mL. In some embodiments, the pH stabilizer comprises a compound selected from Table 3 or a combination thereof.

[124] Radiopharmaceutical compositions described herein can have a suitable pH value. The one or more pH stabilizers can be configured to maintain a pH of the radiopharmaceutical composition at about 3 to about 9, about 4 to about 8, or about 5 to about 7. The pH of the radiopharmaceutical composition can be within a range of about 3 to about 9. The pH of the radiopharmaceutical composition can be within a range of about 4 to about 8. The pH of the radiopharmaceutical composition can be within a range of about 5 to about 7. In some embodiments, the pH of the radiopharmaceutical composition is from about 4.0 to about 9.0, from about 4.5 to about 8.5, from about 5.0 to about 8.0, from about 5.5 to about 7.75, from about 6.0 to about 7.5, from about 6.5 to about 7.25, from 6.75 to about 7.25. The pH of the

radiopharmaceutical composition can be about 4.0 to about 9.0. The pH of the radiopharmaceutical composition can be about 4.5 to about 8.5. The pH of the radiopharmaceutical composition can be about 5.0 to about 8.0. The pH of the radiopharmaceutical composition can be about 5.0 to about 7.0. The pH of the radiopharmaceutical composition can be about 5.5 to about 6.5. The pH of the radiopharmaceutical composition can be about 5.5 to about 6. The pH of the radiopharmaceutical composition can be about 5.6 to about 5.8. The pH of the radiopharmaceutical composition can be about 5.75 to about 5.85. The pH of the radiopharmaceutical composition can be about 5.5 to about 7.75. The pH of the radiopharmaceutical composition can be about 6.0 to about 7.5. The pH of the radiopharmaceutical composition can be about 6.5 to about 7.25. The pH of the radiopharmaceutical composition can be about 6.75 to about 7.25. In some embodiments, the pH of the radiopharmaceutical composition is about 7. In some embodiments, the pH of the radiopharmaceutical composition is about 5.5. In some embodiments, the pH of the radiopharmaceutical composition is about 5.6. In some embodiments, the pH of the radiopharmaceutical composition is about 5.7. In some embodiments, the pH of the radiopharmaceutical composition is about 5.8. In some embodiments, the pH of the radiopharmaceutical composition is about 5.9. In some embodiments, the pH of the radiopharmaceutical composition is about 6. In some embodiments, the pH of the radiopharmaceutical composition is about 6.1. In some embodiments, the pH of the radiopharmaceutical composition is about 6.2.

[125] The radiopharmaceutical composition can comprise one or more radiolysis stabilizers, one or more free metal chelators, and/or one or more pH stabilizers. The radiopharmaceutical composition can comprise one or more radiolysis stabilizers. The radiopharmaceutical composition can comprise one or more free metal chelators. The radiopharmaceutical composition can comprise one or more pH stabilizers.

[126] In some embodiments, a radiopharmaceutical composition described herein comprises: (a) a conjugate (e.g., ^{225}Ac -DOTA-TATE or ^{225}Ac -DOTA-TOC), wherein the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 to 45 mCi/L (e.g., 30 mCi/L); (b) a pH stabilizer, wherein the pH stabilizer is present in the radiopharmaceutical composition at a concentration of about 80 to about 120 mM; (c) optionally a radiolysis stabilizer, wherein the radiolysis stabilizer is present in the radiopharmaceutical composition at concentration of about 1 wt% to about 10wt%; (d) a free metal chelator, therein the free metal chelator is present in the radiopharmaceutical composition at concentration of about 0.01 mg/mL to about 1 mg/mL; and (e) an aqueous vehicle. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 15 to 45

mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 1 to 150 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 5 to 50 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 to 35 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 to 25 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 12 to 23 mCi/L. In some embodiments, a radiopharmaceutical composition described herein comprises: (a) a conjugate (e.g., ^{225}Ac -DOTA-TATE or ^{225}Ac -DOTA-TOC), wherein the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 to 45 mCi/L; (b) a pH stabilizer, wherein the pH stabilizer is sodium L-ascorbate and is present in the radiopharmaceutical composition at a concentration of about 80 to about 120 mM; (c) optionally a radiolysis stabilizer, wherein the radiolysis stabilizer is Dextran 40 and is present in the radiopharmaceutical composition at a concentration of about 1 wt% to about 10wt%; (d) a free metal chelator, wherein the free metal chelator is DTPA and is present in the radiopharmaceutical composition at a concentration of about 0.01 mg/mL to about 1 mg/mL; and (e) an aqueous vehicle, wherein the aqueous vehicle is saline solution. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 15 to 45 mCi/L. In some embodiments, the radiopharmaceutical composition comprises (a) the conjugate, wherein the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 25 to 35 mCi/L; (b) a pH stabilizer, wherein the pH stabilizer is sodium L-ascorbate and is present in the radiopharmaceutical composition at a concentration of about 90-110 mM; (c) a radiolysis stabilizer, wherein the radiolysis stabilizer is Dextran 40 and is present in the radiopharmaceutical composition at a concentration of about 4-6 wt%; (d) a free metal chelator, wherein the free metal chelator is DTPA and is present in the radiopharmaceutical composition at a concentration of about 0.01-0.03 mg/mL; and (e) an aqueous vehicle, wherein the aqueous vehicle is sodium chloride saline solution at a concentration of about 0.9% w/w. In some embodiments, the radiopharmaceutical composition comprises (a) the conjugate, wherein the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 to 25 mCi/L; (b) a pH stabilizer, wherein the pH stabilizer is sodium L-ascorbate and is present in the radiopharmaceutical composition at a concentration of about 90-110 mM; (c) a radiolysis stabilizer, wherein the radiolysis stabilizer is Dextran 40 and is present in the radiopharmaceutical composition at a concentration of about 4-6 wt%; (d) a free metal chelator, wherein the free metal chelator is DTPA and is present in the radiopharmaceutical composition at a concentration of about 0.01-0.03 mg/mL; and (e) an aqueous vehicle, wherein

the aqueous vehicle is sodium chloride saline solution at a concentration of about 0.9% w/w. In some embodiments, the radiopharmaceutical composition comprises (a) the conjugate, wherein the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 25 to 35 mCi/L; (b) a pH stabilizer, wherein the pH stabilizer is sodium L-ascorbate and is present in the radiopharmaceutical composition at a concentration of about 90-110 mM; (c) a free metal chelator, wherein the free metal chelator is DTPA and is present in the radiopharmaceutical composition at a concentration of about 0.04-0.06 mg/mL; and (d) an aqueous vehicle, wherein the aqueous vehicle is sodium chloride saline solution at a concentration of about 0.9% w/w. In some embodiments, the radiopharmaceutical composition comprises (a) the conjugate, wherein the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 to 25 mCi/L; (b) a pH stabilizer, wherein the pH stabilizer is sodium L-ascorbate and is present in the radiopharmaceutical composition at a concentration of about 90-110 mM; (c) a free metal chelator, wherein the free metal chelator is DTPA and is present in the radiopharmaceutical composition at a concentration of about 0.04-0.06 mg/mL; and (d) an aqueous vehicle, wherein the aqueous vehicle is sodium chloride saline solution at a concentration of about 0.9% w/w.

Additional excipients

[127] Radiopharmaceutical compositions described herein can comprise additional excipients. In some embodiments, the additional excipients include excipients suitable for a formulation configured for intravenous administration.

[128] In some embodiments, the radiopharmaceutical composition described herein comprises a surfactant. "Surfactants" can be defined as surface-active amphiphilic compounds such as block co-polymers. They can be referred to as wetting agents. Non-limiting examples of surfactants include a poloxamer (e.g., poloxamer 188), sodium lauryl sulfate, Desoxycholate sodium, Egg yolk phospholipid, Gelatin, Hydrolyzed Lecithin, Polyoxyethylated fatty acid, Polysorbate 80 (Tween 80), Polysorbate 20 (Tween 20), PEG 40 castor oil (polyoxyl 40 castor oil, castor oil POE-40, Croduret 40, polyoxyethylene 40 castor oil, Protachem CA-40), PEG 60 castor oil (Cremophor RH 60, hydrogenated castor oil POE-60, Protachem CAH-60), Poloxamer 188 (Pluronic F68), Povidone (Polyvinyl pyrrolidone, Crosspovidone), Sodium dodecyl sulfate (Na lauryl sulfate), Aluminum monostearate, Sorbitol, and Triton X-100 (Octoxynol-9).

[129] The surfactant used in the present disclosure can comprise a non-ionic surfactant. A non-ionic surfactant has no charged groups in its head. Exemplary nonionic surfactants include, without limitation, fatty alcohols, cetyl alcohol, stearyl alcohol, cetostearyl alcohol, and oleyl alcohol. Exemplary nonionic surfactants include, but are not limited to, polyethylene glycol alkyl ethers (such as octaethylene glycol monododecyl ether, pentaethylene glycol monododecyl ether), polypropylene glycol alkyl ethers, glucoside alkyl ethers (such as decyl glucoside, lauryl

glucoside, octyl glucoside), polyethylene glycol octylphenyl ethers (such as Triton X-100), polyethylene glycol alkylphenyl ethers (such as nonoxynol-9), glycerol alkyl esters (such as glyceryl laurate), polyoxyethylene glycol sorbitan alkyl esters (such as polysorbate), sorbitan alkyl esters (such as Spans), cocamide MEA, cocamide DEA, dodecyltrimethylamine oxide, block copolymers of polyethylene glycol and polypropylene glycol (such as poloxamers), and polyethoxylated tallow amine (POEA). In some embodiments, the surfactant is a non-ionic surfactant that comprises polyethylene glycol. In some embodiments, the surfactant is a block copolymer of polyethylene glycol and polypropylene glycol.

[130] In some embodiments, the non-ionic surfactant has a number average molecular weight of from about 1000 to about 100,000 Da, 2000 to about 20,000 Da, from about 4000 to about 15,000 Da, from about 6000 to about 12,000 Da, or from about 7000 to about 10,000 Da. In some embodiments, the non-ionic surfactant has a number average molecular weight of from about 7000 to about 10,000 Da. In some embodiments, the non-ionic surfactant has an ethylene glycol content of from about 30 wt% to about 99 wt%, from about 50 wt% to about 95 wt%, from about 60 wt% to about 95 wt%, from about 75 wt% to about 90 wt%, or from about 80 wt% to about 85 wt%. In some embodiments, the non-ionic surfactant has an ethylene glycol content of from about 80 wt% to about 85 wt%.

[131] The surfactant used in the present disclosure can comprise a cationic surfactant. Cationic surfactants include pH-dependent primary, secondary, or tertiary amines such as octenidine dihydrochloride; and permanently charged quaternary ammonium salts such as cetyltrimonium bromide (CTAB), cetylpyridinium chloride (CPC), benzalkonium chloride (BAC), benzethonium chloride (BZT), dimethyldioctadecylammonium chloride, and dioctadecyldimethylammonium bromide (DODAB).

[132] The surfactant used in the present disclosure can comprise an anionic surfactant. Anionic surfactants contain anionic functional groups at their head, such as sulfate, sulfonate, phosphate, and carboxylates. Exemplary anionic surfactants include, but are not limited to, ammonium lauryl sulfate, sodium lauryl sulfate (sodium dodecyl sulfate, SLS, or SDS), and the related alkyl-ether sulfates sodium laureth sulfate (sodium lauryl ether sulfate or SLES), sodium myreth sulfate, docusate (dioctyl sodium sulfosuccinate), perfluorooctanesulfonate (PFOS), perfluorobutanesulfonate, alkyl-aryl ether phosphates, and alkyl ether phosphates.

[133] The surfactant used in the present disclosure can be a zwitterionic surfactant. Zwitterionic (amphoteric) surfactants refer to those having cationic and anionic centers attached to the same molecule. Exemplary zwitterionic surfactants include, without limitation, phospholipids phosphatidylserine, phosphatidylethanolamine, phosphatidylcholine, and sphingomyelins.

[134] In some embodiments of the present disclosure, the concentration of a surfactant described herein in the described liquid pharmaceutical composition is 0.1% to 15% by weight. In some embodiments, the concentration of the surfactant is 0.5%-8% by weight in the liquid pharmaceutical composition. In some embodiments, the concentration of the surfactant is 0.5%-6% by weight in the liquid pharmaceutical composition. In some embodiments, the concentration of the surfactant is 0.25%-8% by weight in the liquid pharmaceutical composition. In some embodiments, the concentration of the surfactant is 0.75%-8% by weight in the liquid pharmaceutical composition. In some embodiments, the concentration of the surfactant is 0.5%-5% by weight in the liquid pharmaceutical composition. In some embodiments, the concentration of the surfactant is 0.75%-10% by weight in the liquid pharmaceutical composition. In some embodiments, the concentration of the surfactant is 0.75%-6% by weight in the liquid pharmaceutical composition. In some embodiments, the concentration of the surfactant is 0.75%-4% by weight in the liquid pharmaceutical composition. In some embodiments, the concentration of the surfactant is 1%-4% by weight in the liquid pharmaceutical composition. In some embodiments, the concentration of the surfactant is 1%-6% by weight in the liquid pharmaceutical composition. In some embodiments, the concentration of the surfactant is 5%-10% by weight in the liquid pharmaceutical composition. In some embodiments, the concentration of the surfactant is 5%-15% by weight in the liquid pharmaceutical composition. In some embodiments, the concentration of the surfactant is 10%-25% by weight in the liquid pharmaceutical composition.

[135] In some embodiments, the radiopharmaceutical composition described herein comprises a tonicity adjusting agent. Exemplary tonicity adjusting agents include dextrose, glycerin, mannitol, potassium chloride and sodium chloride.

[136] In some embodiments, the radiopharmaceutical composition described herein comprises a special additive. In some embodiments, the special additive comprises Acetyl tryptophan, Aluminum hydroxide, Aluminum phosphate, Aluminum potassium sulfate, Amino acids (leucine, isoleucine, lysine (as acetate or HCl salt), valine, phenylalanine, threonine, tryptophan, alanine, aspartic acid, glutamic acid, proline, serine, tyrosine, taurine), ϵ -Aminocaproic acid, Calcium D-saccharate, Caprylate sodium, 8-Chlorotheophylline, Creatine, Creatinine, Cholesterol, Cholesteryl sulfate sodium, Cyclohexanedione dioxime, Diethanolamine, Distearyl phosphatidylcholine, Distearyl phosphatidylglycerol, L-alpha-dimyristoylphosphatidylcholine, L-alpha-dimyristoylphosphatidylglycerol, Dioleoylphosphatidylcholine (DOPC), Dipalmitoylphosphatidylglycerol (DPPG), (R)-hexadecanoic acid, 1-[(phosphonoxy)methyl]-1,2-ethanediyl ester, monosodium salt (DPPA), (R)-4-hydroxy-N,N,N-trimethyl-10-oxo-7-[(1oxohexadecyl)oxy]-3,4,9-trioxa-4-

phosphapentacosan-1-aminium, 4-oxide, inner salt (DPPC), (R)-[6-hydroxy-6-oxido-9-[(1-oxohexadecyl)oxy]-5,7,11-trioxa-2aza-6-phosphahexacos-1-yl]- ω -methoxypoly(ox-1,2-ethanediyl), monosodium salt (MPEG5000 DPPE), MPEG-distearoyl phosphoethanolamine, Ethyl lactate, Ethylenediamine, L-Glutamate sodium, Hyaluronate sodium, Hydrogenated soy phosphatidylcholine, Iron ammonium citrate, Lactic acid, D,L-lactic and glycolic acid copolymer, Meglumine, Methyl boronic acid, Niacinamide, Paraben methyl, Phosphatidylglycerol, egg (EPG), Potassium sodium tartrate, Protamine (as sulfate), Simethicone, Saccharin sodium, Sodium D-gluconate, Sodium hypochlorite, Sodium sulfate, Stannous chloride, Sulfosalicylate disodium, Tin chloride (stannous and stannic), Tri-n-butyl phosphate, Tricaprylin, Triolein, von Willebrand factor, Zinc, Zinc acetate, Zinc carbonate, Zinc oxide, or a combination thereof.

[137] In some embodiments, the radiopharmaceutical composition described herein comprises a suspending agent. Non-limiting examples of suspending agents include Carboxy methyl cellulose (CMC), Croscarmellose sodium, sodium CMC, xanthan gum, hydroxyl ethyl cellulose (HEC), hydroxyl propyl methyl cellulose (HPMC), and Avicel CL-611. Further exemplary suspending agents include carboxymethylcellulose (sodium and other salts), carboxy-vinyl copolymers, carboxymethyl hydroxyethylcellulose, cellulose, such as microcrystalline cellulose, combinations of microcrystalline cellulose with sodium carboxymethylcellulose (such as Avicel RC-501, RC-581, RC-591, and CL-611), hydrophobically modified hydroxyethyl cellulose, hydroxyethyl cellulose, hydroxypropyl guar, hydroxypropyl methylcellulose (such as Benecel K750 ® or Benecel K1500®), hydroxypropyl cellulose, methyl cellulose, natural gums and their derivatives, xanthan gum, guar gum, gum Arabic, partially and fully hydrolyzed polyvinyl alcohols, partially neutralized polyacrylic acid, polyalkylene glycol, polysaccharide gums, polyvinylpyrrolidone and derivatives thereof, starch and its derivatives, vinylpyrrolidone homo- and copolymers, water-soluble cellulose ethers, and the mixtures thereof.

[138] These compositions can be sterilized by conventional sterilization techniques. The resulting aqueous solutions may be packaged for use or filtered under aseptic conditions and lyophilized. The lyophilized preparation can be combined with a sterile aqueous solution prior to administration. The compositions can contain pharmaceutically acceptable auxiliary substances as appropriate to approximate physiological conditions, such as tonicity adjusting agents and the like, for example, sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, sodium lactate, sorbitan monolaurate, triethanolamine oleate, etc. Pharmaceutical compositions can be selected according to their physical characteristic, including, but not limited to fluid volumes, viscosities and other parameters in accordance with the particular mode of administration selected.

Conjugate

[139] In one aspect, provided herein is a radiopharmaceutical composition comprising a conjugate or pharmaceutically acceptable salts or solvates thereof described herein. The radiopharmaceutical composition can further comprise a pharmaceutically acceptable carrier such as an aqueous vehicle. Normal saline can be employed as the pharmaceutically acceptable carrier. Other suitable carriers or aqueous vehicles can include, e.g., water, buffered water, 0.9% isotonic saline, 0.4% saline, 0.3% glycine, and the like, including glycoproteins for enhanced stability, such as albumin, lipoprotein, globulin, etc. In some embodiments, the aqueous vehicle is water for injection. In some embodiments, the aqueous vehicle is 0.9% w/w sodium chloride saline solution. In some embodiments, the conjugate is ^{225}Ac -DOTA-TATE, ^{225}Ac -DOTA-TOC, ^{225}Ac -HA-DOTA-TATE, or ^{225}Ac -DOTA-JR-11.

[140] The amount of conjugates administered can depend upon the particular targeting moiety used, the disease state being treated, the therapeutic agent being delivered, and the judgment of the clinician.

[141] The concentration of the conjugates or pharmaceutically acceptable salts or solvates thereof described herein in the pharmaceutical formulations can vary. In some embodiments, the conjugate is present in the pharmaceutical composition from about 0.05% to about 1% by weight, about 1% to about 2% by weight, about 2% to about 5% by weight, about 5% to about 10% by weight, about 10% to about 30% by weight, about 30% to about 50% by weight, about 50% to about 75% by weight, or about 75% to about 99% by weight. In some embodiments, the conjugate is present in the pharmaceutical composition from about 0.05% to about 1% by weight. In some embodiments, the conjugate is present in the pharmaceutical composition from about 0.1% to about 5% by weight.

[142] In some embodiments, the conjugate is present in the pharmaceutical composition in an amount that provides a radioactivity of about 0.5 to about 1000 $\mu\text{Ci/ml}$. In some embodiments, the conjugate is present in the pharmaceutical composition in an amount that provides a radioactivity of about 1 to about 15 $\mu\text{Ci/ml}$, about 2 to about 20 $\mu\text{Ci/ml}$, about 5 to about 50 $\mu\text{Ci/ml}$, about 10 to about 100 $\mu\text{Ci/ml}$, about 20 to about 200 $\mu\text{Ci/ml}$, about 50 to about 500 $\mu\text{Ci/ml}$, about 100 to about 250 $\mu\text{Ci/ml}$, about 5 to about 25 $\mu\text{Ci/ml}$, about 10 to about 30 $\mu\text{Ci/ml}$, or about 5 to about 15 $\mu\text{Ci/ml}$. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 5 to 20 $\mu\text{Ci/mL}$. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 5 to 45 $\mu\text{Ci/mL}$. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 1 to 100 $\mu\text{Ci/mL}$. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration

equivalent to about 15 to 45 $\mu\text{Ci/mL}$. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 to 35 $\mu\text{Ci/mL}$. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 to 25 $\mu\text{Ci/mL}$. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 12 to 23 $\mu\text{Ci/mL}$. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 to 200 $\mu\text{Ci/mL}$. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 100 to 500 $\mu\text{Ci/mL}$. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 100 to 1000 $\mu\text{Ci/mL}$. In some embodiments, the conjugate is present in the pharmaceutical composition in an amount that provides a radioactivity of at most about 5, 10, 15, 50, 75, 100, 200, or 500 $\mu\text{Ci/mL}$. In some embodiments, the conjugate is present in the pharmaceutical composition in an amount that provides a radioactivity of at most about 500, 600, 700, 800, 900, or 1000 $\mu\text{Ci/mL}$. In some embodiments, the conjugate is present in the pharmaceutical composition in an amount that provides a radioactivity of at most about 15 $\mu\text{Ci/mL}$. In some embodiments, the conjugate is present in the pharmaceutical composition in an amount that provides a radioactivity of about 1 to 15 $\mu\text{Ci/mL}$. In some embodiments, the conjugate is present in the pharmaceutical composition in an amount that provides a radioactivity of at most about 35 $\mu\text{Ci/mL}$. In some embodiments, the conjugate is present in the pharmaceutical composition in an amount that provides a radioactivity of about 1 to 35 $\mu\text{Ci/mL}$. In some embodiments, the conjugate is present in the pharmaceutical composition in an amount that provides a radioactivity of at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, or 50 $\mu\text{Ci/mL}$. In some embodiments, the conjugate is present in the pharmaceutical composition in an amount that provides a radioactivity of at most about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 50, 75, 100, 125, 150 or 200 $\mu\text{Ci/mL}$.

[143] In some embodiments, the conjugate is present in the pharmaceutical composition in an amount that provides a radioactivity of about 0.5 to about 1000 mCi/L . In some embodiments, the conjugate is present in the pharmaceutical composition in an amount that provides a radioactivity of about 1 to about 15 mCi/L , about 2 to about 20 mCi/L , about 5 to about 50 mCi/L , about 10 to about 100 mCi/L , about 20 to about 200 mCi/L , about 50 to about 500 mCi/L , about 100 to about 250 mCi/L , about 5 to about 25 mCi/L , about 10 to about 30 mCi/L , or about 5 to about 15 mCi/L . In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 5 to 20 mCi/L . In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 5 to 45 mCi/L . In some embodiments, the conjugate is present in the radiopharmaceutical composition at a

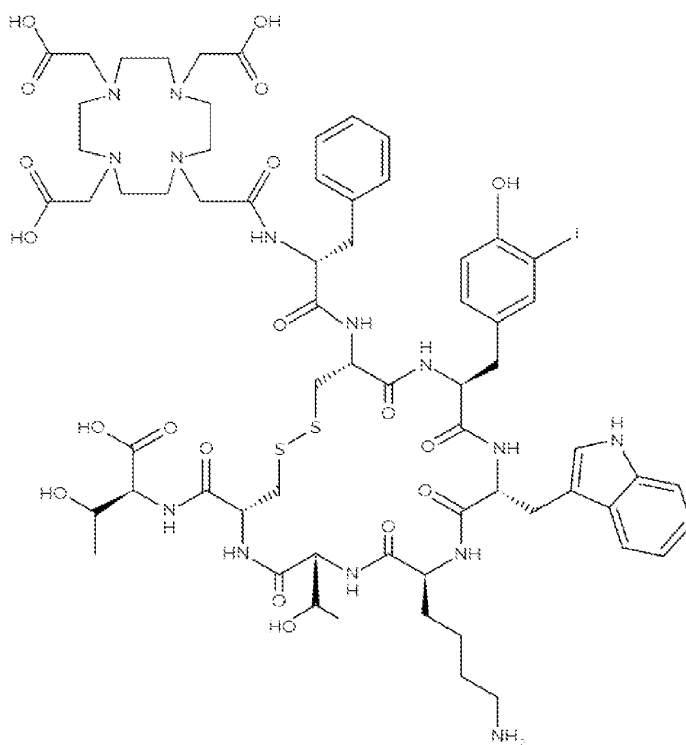
concentration equivalent to about 1 to 100 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 15 to 45 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 to 35 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 to 25 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 12 to 23 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 to 200 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 100 to 500 mCi/L. In some embodiments, the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 100 to 1000 mCi/L. In some embodiments, the conjugate is present in the pharmaceutical composition in an amount that provides a radioactivity of at most about 5, 10, 15, 50, 75, 100, 200, or 500 mCi/L. In some embodiments, the conjugate is present in the pharmaceutical composition in an amount that provides a radioactivity of at most about 500, 600, 700, 800, 900, or 1000 mCi/L. In some embodiments, the conjugate is present in the pharmaceutical composition in an amount that provides a radioactivity of at most about 15 mCi/L. In some embodiments, the conjugate is present in the pharmaceutical composition in an amount that provides a radioactivity of about 1 to 15 mCi/L. In some embodiments, the conjugate is present in the pharmaceutical composition in an amount that provides a radioactivity of at most about 35 mCi/L. In some embodiments, the conjugate is present in the pharmaceutical composition in an amount that provides a radioactivity of about 1 to 35 mCi/L. In some embodiments, the conjugate is present in the pharmaceutical composition in an amount that provides a radioactivity of at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, or 50 mCi/L.

[144] A composition described herein can comprise a conjugate, or a pharmaceutically acceptable salt or solvate thereof, that comprises actinium-225. In some embodiments, actinium-225 is present in a herein-described radiopharmaceutical composition that it provides a volumetric radioactivity of about 0.005 to 1000 MBq/mL. In some embodiments, the actinium-225 is present in a herein-described radiopharmaceutical composition that it provides a volumetric radioactivity of about 0.5 to 20 MBq/mL. In some embodiments, the actinium-225 is present in a herein-described radiopharmaceutical composition that it provides a volumetric radioactivity of about 0.4 to 20 MBq/mL. In some embodiments, the actinium-225 is present in a herein-described radiopharmaceutical composition that it provides a volumetric radioactivity of about 0.2 to 5 MBq/mL. In some embodiments, the actinium-225 is present in a herein-described radiopharmaceutical composition that it provides a volumetric radioactivity of about 0.4 to 1

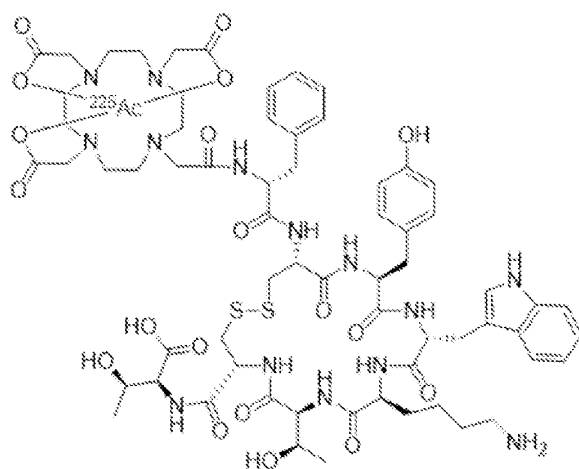
MBq/mL. In some embodiments, actinium-225 is present in a herein-described radiopharmaceutical composition that it provides a volumetric radioactivity of about 0.1 to 100 MBq/mL. In some embodiments, actinium-225 is present in a herein-described radiopharmaceutical composition that it provides a volumetric radioactivity of about 0.1 to 100, about 0.1 to 50, about 0.1 to 25, about 0.1 to 10, about 0.1 to 5, about 1 to 100, about 0.5 to 10, about 0.5 to 50, about 10 to 100, about 10 to 50, about 10 to 20, about 1 to 10, or about 1 to 20 MBq/mL. In some embodiments, actinium-225 is present in a herein-described radiopharmaceutical composition that it provides a volumetric radioactivity of about 0.1, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 or 30 MBq/mL. In some embodiments, actinium-225 is present in a herein-described radiopharmaceutical composition that it provides a volumetric radioactivity of at least about 0.001, 0.01, 0.1, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 MBq/mL. In some embodiments, actinium-225 is present in a herein-described radiopharmaceutical composition that it provides a volumetric radioactivity of at most about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40 or 50 MBq/mL. In some embodiments, a composition described herein has a total DOTA-TATE peptide concentration of ≤ 11.5 $\mu\text{g/mL}$ (including e.g., unlabeled DOTATATE, ^{225}Ac -DOTATATE, and metal-DOTATATE species). In some embodiments, a composition described herein has a total DOTA-TATE peptide concentration of at most about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 50 $\mu\text{g/mL}$. In some embodiments, a composition described herein has a total DOTA-TATE peptide concentration of at least about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 $\mu\text{g/mL}$.

[145] The composition described herein can comprise a conjugate, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient or carrier. The conjugate as described can be substantially pure, in that it contains less than about 10%, less than about 5%, or less than about 1%, or less than about 0.1% by weight, of other organic small molecules, such as unreacted intermediates or synthesis by-products that are created, for example, in one or more of the steps of a synthesis method. The conjugate can be ^{225}Ac -DOTA-TATE, ^{225}Ac -DOTA-TOC, or ^{225}Ac -DOTA-JR-11. The conjugate can be ^{225}Ac -DOTA-TATE. The conjugate can be ^{225}Ac -DOTA-TOC. The conjugate can be ^{225}Ac -DOTA-JR-11. In some embodiments, the conjugate is ^{225}Ac -high-affinity DOTATATE (or ^{225}Ac -HA-DOTATATE). In

some embodiments, HA-DOTATATE is illustrated by the following structure

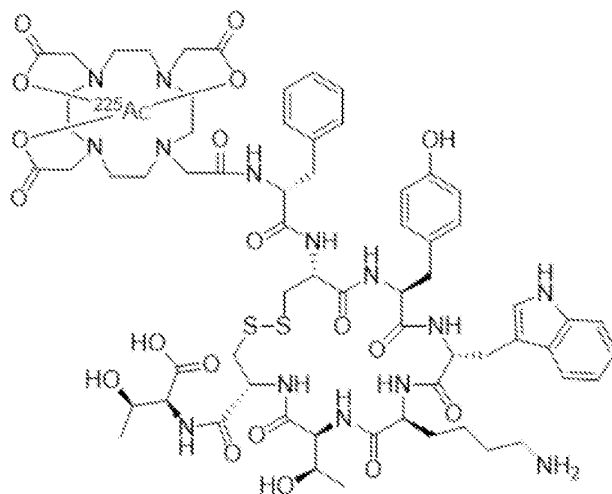


[146] ^{225}Ac -DOTA-TATE can be illustrated as having the following structure:



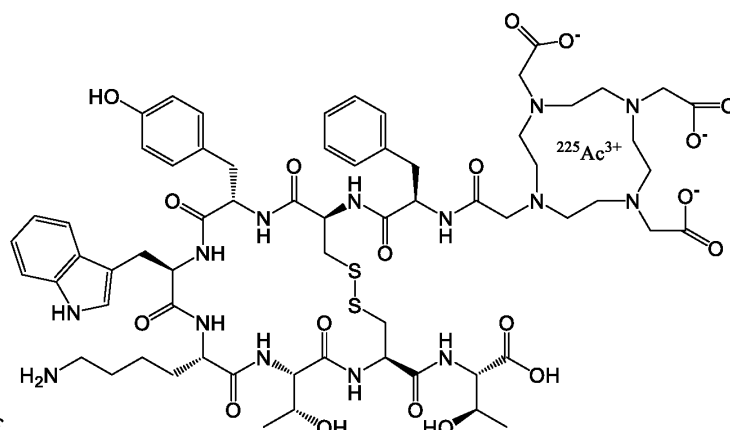
The IUPAC Name for ^{225}Ac -DOTA-TATE is: (2,2',2''-(10-(2-(((R)-1-(((4R,7S,10S,13R,16S,19R)-13-((1H-indol-3-yl)methyl)-10-(4-aminobutyl)-4-(((1S,2R)-1-carboxy-2-hydroxypropyl)carbamoyl)-16-(4-hydroxybenzyl)-7-((R)-1-hydroxyethyl)-6,9,12,15,18-pentaoxo-1,2-dithia-5,8,11,14,17-pentaazacycloicosan-19-yl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-1,4,7-triyl)triacetate;actinium-225(3+)).

[147] In some embodiments, provided herein is a pharmaceutical composition comprising a

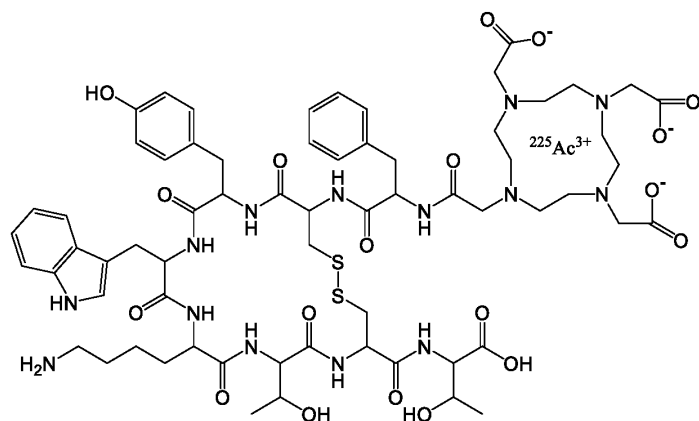


conjugate that is , and one or more stabilizing agents.

[148] In some embodiments, provided herein is a pharmaceutical composition comprising a



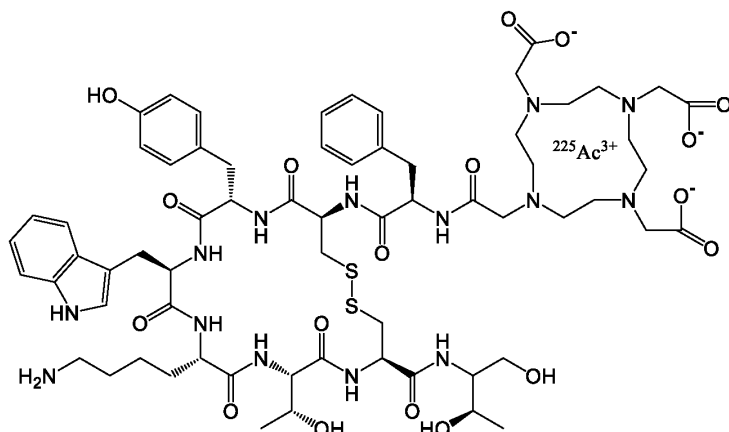
conjugate that has a structure of , and one or more stabilizing agents. In some embodiments, provided herein is a pharmaceutical composition comprising a conjugate that has a structure of



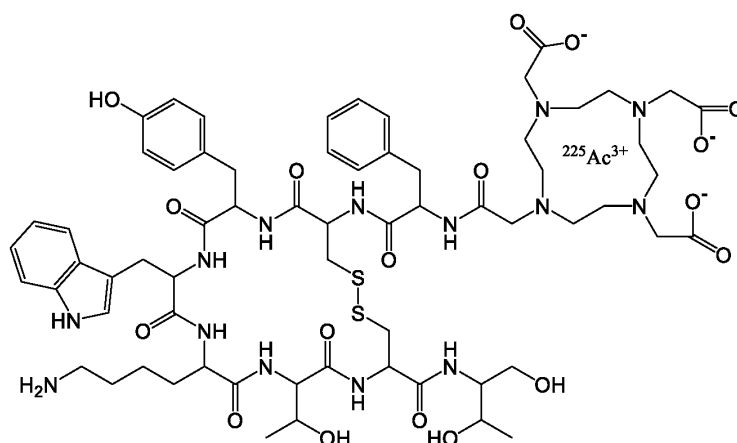
, and one or more stabilizing agents.

It is understood that the chelation between ^{225}Ac and the metal chelator is not shown in the above

two structures. In some embodiments, for example in acidic aqueous conditions, the radionuclide actinium-225 exists in a salt form, e.g., as $^{225}\text{Ac}^{3+}$. In some embodiments, the conjugate is in a salt form. In some embodiments, the conjugate is an acetate salt. In some embodiments, provided herein is a pharmaceutical composition comprising a conjugate that is



, and one or more stabilizing agents. In some embodiments, provided herein is a pharmaceutical composition comprising a



conjugate that is , and one or more stabilizing agents. It is understood that the chelation between ^{225}Ac and the metal chelator is not shown in the above two structures. In some embodiments, for example in acidic aqueous conditions, the radionuclide actinium-225 exists in a salt form, e.g., as $^{225}\text{Ac}^{3+}$. In some embodiments, the conjugate is in a salt form. In some embodiments, the conjugate is an acetate salt. A person of ordinary skill would appreciate that the dissociation of an acid can depend on the pH value of the environment and its pK value. Accordingly, in some embodiments, a conjugate described herein can exist in a completely ionized, partially ionized or non-ionized form.

Targeting ligand

[149] In one aspect, provided herein is a radiopharmaceutical composition comprising a conjugate or pharmaceutically acceptable salts or solvates thereof. In some embodiments, the conjugate described herein comprises a targeting ligand and a metal chelator.

[150] The targeting ligand described herein can bind to one or more target within a subject's system or an in vitro system. The targeting ligand can target a protein, a receptor on a cell, or other chemical moiety that can perform signaling functions within the subject's system. The targeting ligand can bind to a receptor on the surface of a cell within the subject's system. In some embodiments, the targeting ligand binds to a somatostatin receptor (SSR). An SSR can be a mammalian SSR. A mammalian SSR can be a human SSR. A human SSR can comprise somatostatin receptor type 1 (SSTR1), somatostatin receptor type 2 (SSTR2), somatostatin receptor type 3 (SSTR3), somatostatin receptor type 4 (SSTR4), and/or somatostatin receptor type 5 (SSTR5). An SSR can be a human somatostatin receptor type 2 (SSTR2). In some embodiments, the targeting ligand binds to a human somatostatin receptor type 2 (SSTR2). The targeting ligand can comprise a peptide and/or a small molecule compound. The targeting ligand can comprise an agonist of the SSR. The targeting ligand can comprise an antagonist of the SSR. The agonist of the SSR can comprise a partial agonist of the SSR. The agonist of the SSR can comprise a full agonist of the SSR. The agonist of the SSR can comprise an inverse agonist of the SSR. The antagonist of the SSR can comprise a competitive antagonist of the SSR. The targeting ligand can comprise an allosteric modulator of the SSR. The allosteric modulator of the SSR can be an allosteric agonist of SSR. The allosteric modulator of the SSR can be an allosteric antagonist of SSR.

[151] The targeting ligand described herein can comprise one or more peptides, which can be the same or different. The peptide can be linear or cyclic. The peptide can be monocyclic. The peptide can comprise a binding peptide. The binding peptide can bind to one or more target within a subject's system or an in vitro system. The binding peptide can bind to a somatostatin receptor (SSR). The binding peptide can bind to a somatostatin receptor type 1 (SSTR1), somatostatin receptor type 2 (SSTR2), somatostatin receptor type 3 (SSTR3), somatostatin receptor type 4 (SSTR4), and/or somatostatin receptor type 5 (SSTR5). The binding peptide can bind to a somatostatin receptor type 2 (SSTR2). The binding peptide can bind to a human somatostatin receptor type 2 (SSTR2).

[152] The peptide can comprise any suitable number of amino acid residues. The peptide can comprise from 4 to 50, 5 to 40, 6 to 30, 7 to 20, or 8 to 10 amino acid residues. The peptide can comprise from 6 to 14 amino acid residues. The peptide can comprise from 6 to 10 amino acid residues. The peptide can comprise from 7 to 9 amino acid residues. The peptide can comprise 8 to 9 amino acid residues. The peptide can comprise 14 amino acid residues. The peptide can comprise 13 amino acid residues. The peptide can comprise 12 amino acid residues. The peptide can comprise 11 amino acid residues. The peptide can comprise 10 amino acid residues. The peptide can comprise 9 amino acid residues. The peptide can comprise 8 amino acid residues. The

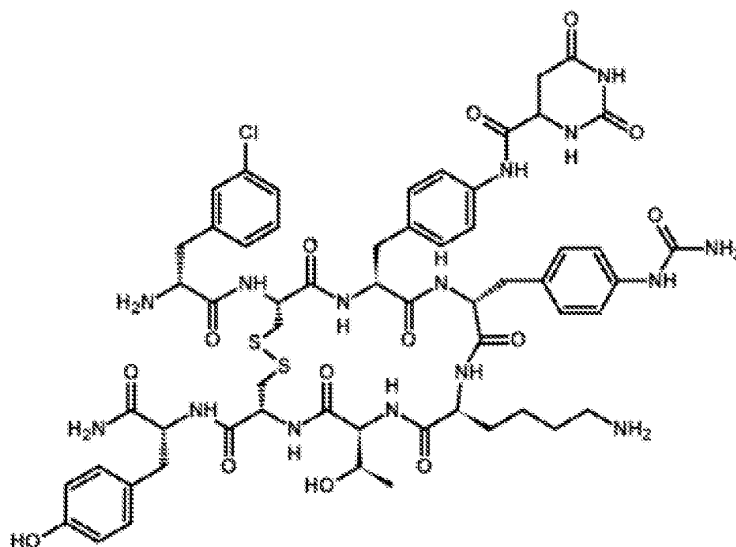
peptide can comprise 7 amino acid residues. The peptide can comprise 6 amino acid residues. The peptide can consist of 10 amino acid residues. The peptide can consist of 14 amino acid residues. The peptide can consist of 13 amino acid residues. The peptide can consist of 12 amino acid residues. The peptide can consist of 11 amino acid residues. The peptide can consist of 10 amino acid residues. The peptide can consist of 9 amino acid residues. The peptide can consist of 8 amino acid residues. The peptide can consist of 7 amino acid residues. The peptide can consist of 6 amino acid residues. The conjugate can comprise a monocyclic peptide of 6, 7, 8, 9, 10, 11, 12, 13, or 14 amino acid residues. The amino acid residues described herein can be modified to remove or add one or more functional groups.

[153] A targeting ligand described herein can be a cyclized peptide. Cyclization can be achieved via a single disulfide bond or via a peptide bond, alkyl bond, alkenyl bond, ester bond, thioester bond, ether bond, thioether bond, phosphate ether bond, azo bond, C—S—C bond, C—N—C bond, C=N—C bond, C=N—O bond, amide bond, lactam bridge, carbamoyl bond, urea bond, thiourea bond, amine bond, thioamide bond, or the like, but not limited to them. The peptide can comprise a cyclic peptide that is cyclized by a peptide bond. A cyclization of a peptide can stabilize the peptide structure and thereby enhance affinity for a target. The cyclization can occur between the N- and C-terminus, or it can occur between a terminal amino acid and a non-terminal amino acid. The cyclization can occur between two non-terminal amino acids. The peptide can be cyclized via one or more cysteines. The peptide can comprise a cysteine at the C-terminus. The peptide can comprise a cysteine at the N-terminus. The cyclization can occur via a disulfide bond between cysteines or between cysteine and another thiol group-bearing residue.

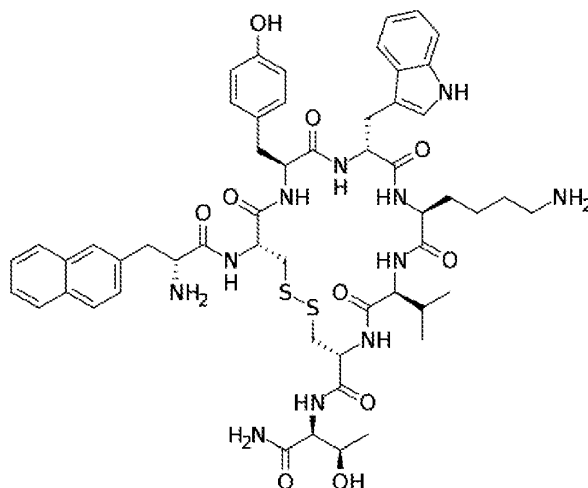
[154] Exemplary targeting ligands include BMS-753493, Somatostatins or somatotropin release inhibiting factor (SRIF), SRIF-14, SRIF-28, Octreotide, Octreotate, Lanreotide, Pasireotide, JR11, L-779,976, BIM-23120, Satoreotide, depreotide, 18F-KYNDRLPLYISNP (SEQ ID NO: 103), CaIX-P1, and FAP-2286. The targeting ligand can comprise octreotate, octreotide, D-Phe1-cyclo(Cys2-Tyr3-D-Trp4-Lys5-Thr6-Cys7)Thr8 (SEQ ID NO: 97) (tyr3-octreotate or TATE), D-Phe1-cyclo(Cys2-Tyr3-D-Trp4-Lys5-Thr6-Cys7)Thr(ol)8 (SEQ ID NO: 98) (Phe1-Tyr3octreotide, edotreotide, or TOC), D-Phe1-cyclo(Cys2-Phe3-D-Trp4-Lys5-Thr6-Cys7)Thr(ol)8 (SEQ ID NO: 99) (OC), D-Phe1-cyclo(Cys2-1-Nal-D-Trp4-Lys5-Thr6-Cys7)Thr(ol)8 (SEQ ID NO: 100) (NOC), p-Cl-Phe-cyclo(D-Cys-Aph(Hor)-D-Aph(Cbm)-Lys-Thr-Cys)D-Tyr-NH2 (SEQ ID NO: 101) (JR11), or p-Cl-Phe-cyclo(D-Cys-Tyr-D-Aph(Cbm)-Lys-Thr-Cys)-D-Tyr-NH2 (SEQ ID NO: 102) (LM3). The targeting ligand can be tyr3-octreotate, edotreotide, octreotate, or octreotide. The targeting ligand can be tyr3-octreotate. In some embodiments, the targeting ligand is 3-iodo-Tyr3-octreotate. In some embodiments, the targeting ligand is TATE. In some embodiments, the targeting ligand is TOC. In some embodiments, the

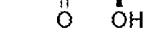
targeting ligand is NOC. In some embodiments, the targeting ligand is JR-11. In some embodiments, the targeting ligand is Lanreotide. In some embodiments, the targeting ligand is Pasireotide. In some embodiments, the targeting ligand is OC. In some embodiments, the targeting ligand is NOC. In some embodiments, the targeting ligand is LM3. In some embodiments, the targeting ligand is satoreotide. In some embodiments, the targeting ligand is depreotide.

[155] In some embodiments, a conjugate described herein comprises a targeting ligand that



has a structure of  (JR-11 or Satoreotide). In some embodiments, a conjugate described herein comprises a targeting ligand that



has a structure of  (Lanreotide).

[156] In some embodiments, a conjugate described herein comprises a targeting ligand, wherein the targeting ligand is a binding peptide (e.g., a peptide selected from Table 4). The binding peptide can comprise an amino acid sequence with at least 70% identity to a sequence selected from SEQ IDs 1 to 96. The binding peptide can comprise an amino acid sequence with at least 75% identity to a sequence selected from SEQ IDs 1 to 96. The binding peptide can

comprise an amino acid sequence with at least 80% identity to a sequence selected from SEQ IDs 1 to 96. The binding peptide can comprise an amino acid sequence with at least 85% identity to a sequence selected from SEQ IDs 1 to 96. The binding peptide can comprise an amino acid sequence with at least 85% identity to a sequence selected from SEQ IDs 1 to 96. The binding peptide can comprise an amino acid sequence with at least 90% identity to a sequence selected from SEQ IDs 1 to 96. The binding peptide can comprise an amino acid sequence with at least 95% identity to a sequence selected from SEQ IDs 1 to 96. The binding peptide can comprise an amino acid sequence with at least 98% identity to a sequence selected from SEQ IDs 1 to 96. The binding peptide can comprise an amino acid sequence with at least 99% identity to a sequence selected from SEQ IDs 1 to 96. The binding peptide can comprise an amino acid sequence an amino acid sequence selected from SEQ IDs 1 to 96, as listed in **Table 4**.

Table 4. Sequence ID List

SEQ ID	Sequences
1	H- ^D Phe-c[Cys-Tyr- ^D Trp-Lys-Val-Cys]-Trp-OH
2	H- ^D 3Pal-c[Cys-Tyr- ^D Trp-Lys-Val-Cys]-Thr-OH
3	H- ^D Phe-c[Cys-Phe- ^D Trp-Lys-Thr-Cys]-Thr[ol]
4	H-Nal-c[^D Cys-3Pal- ^D Trp-Lys-Ala-Cys]-Nal-OH
5	H-Nal-c[^D Cys-3Pal- ^D Trp-Lys-Gly-Cys]-Nal-OH
6	H-Nal-c[^D Cys-3Pal- ^D Trp-Lys-Ile-Cys]-Nal-OH
7	H-Nal-c[^D Cys-3Pal- ^D Trp-Lys-Leu-Cys]-Nal-OH
8	H-Nal-c[^D Cys-3Pal- ^D Trp-Lys-Val-Cys]-Nal-OH
9	H-c[Cys-Lys-Phe-Phe- ^D Trp-Amp-Thr-Phe-Thr-Ser-Cys]-OH
10	H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-Met-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-c[Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys]-OH
11	H-c[Cys-Phe-Phe-Trp-Lys-Thr-Phe-Cys]-OH (OLT-8)
12	H-c[Cys-Phe-Phe- ^D Trp-Lys-Thr-Phe-Cys]-OH (O ^D T-8)
13	H-c[Cys- ^L Agl(N ^β Me,benzoyl)-Phe- ^D Trp-Lys-Thr-Phe-Cys]-OH
14	H-c[Cys- ^D Agl(N ^β Me,benzoyl)-Phe- ^D Trp-Lys-Thr-Phe-Cys]-OH
15	H-c[Cys-Phe- ^L Agl(N ^β Me,benzoyl)-Trp-Lys-Thr-Phe-Cys]-OH
16	H-c[Cys-Phe- ^D Agl(N ^β Me,benzoyl)-Trp-Lys-Thr-Phe-Cys]-OH
17	H-c[Cys-Phe- ^L Agl(N ^β Me,benzoyl)- ^D Trp-Lys-Thr-Phe-Cys]-OH
18	H-c[Cys-Phe- ^D Agl(N ^β Me,benzoyl)- ^D Trp-Lys-Thr-Phe-Cys]-OH
19	H-c[^D Cys-Phe- ^L Agl(N ^β Me,benzoyl)- ^D Trp-Lys-Thr-Phe-Cys]-OH
20	H-c[^D Cys-Phe- ^D Agl(N ^β Me,benzoyl)- ^D Trp-Lys-Thr-Phe-Cys]-OH
21	H-Tyr-c[Cys-Phe- ^L Agl(N ^β Me,benzoyl)-Trp-Lys-Thr-Phe-Cys]-OH
22	H-Tyr-c[Cys-Phe- ^D Agl(N ^β Me,benzoyl)-Trp-Lys-Thr-Phe-Cys]-OH

23	H-Tyr-c[Cys-Phe- ^L Agl(N ^β Me,benzoyl)- ^D Trp-Lys-Thr-Phe-Cys]-OH
24	H-Tyr-c[Cys-Phe- ^D Agl(N ^β Me,benzoyl)- ^D Trp-Lys-Thr-Phe-Cys]-OH
25	H-c[Cys-Phe-Phe- ^D Trp- ^L Agl(^β Ala)-Thr-Phe-Cys]-OH
26	H-c[Cys-Phe-Phe- ^D Trp- ^D Agl(^β Ala)-Thr-Phe-Cys]-OH
27	H-c[Cys-Phe-Phe- ^D Trp- ^L Agl(N ^β Me, ^β Ala)-Thr-Phe-Cys]-OH
28	H-c[Cys-Phe-Phe- ^D Trp- ^D Agl(N ^β Me, ^β Ala)-Thr-Phe-Cys]-OH
29	H-c[Cys-Phe-Phe- ^D Trp-Lys- ^L Agl(N ^β Me,HO-Ac)-Phe-Cys]-OH
30	H-c[Cys-Phe-Phe- ^D Trp-Lys- ^D Agl(N ^β Me,HO-Ac)-Phe-Cys]-OH
31	H-c[Cys-Phe-Phe- ^D Trp-Lys-Thr- ^L Agl(N ^β Me,benzoyl)-Cys]-OH
32	H-c[Cys-Phe-Phe- ^D Trp-Lys-Thr- ^L Agl(N ^β Me,benzoyl)-Cys]-OH
33	H-c[Cys-Phe-Phe- ^D Trp-Lys-Thr-Tyr-Cys]-OH
34	H-c[Cys-Phe-Phe-Trp-Lys-Thr-Tyr-Cys]-OH
35	H-c[Cys-Phe-Xle-Trp-Lys-Thr-Phe-Cys]-OH
36	H-c[Cys-Phe-Tyr- ^D Trp-Lys-Thr-Phe-Cys]-OH
37	H-c[Cys-Phe-Tyr-Trp-Lys-Thr-Phe-Cys]-OH
38	H-Tyr-c[Cys-Phe-Ala- ^D Trp-Lys-Thr-Phe-Cys]-OH
39	H-Tyr-c[Cys-Phe-Ala-Trp-Lys-Thr-Phe-Cys]-OH
40	H-Tyr-c[Cys-Phe-Phe-Trp-Lys-Thr-Phe-Cys]-OH
41	H-Tyr-c[Cys-Phe-Xle-Trp-Lys-Thr-Phe-Cys]-OH
42	H-Ala-Gly-c[Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys]-OH
43	H-c[Cys-Phe-Ala- ^D Trp-Lys-Thr-Ala-Cys]-OH
44	H-c[Cys-Phe-Ala- ^D Trp-Lys-Thr-Phe-Cys]-OH
45	H-c[Cys-Phe-Phe- ^D Trp-Lys-Thr-Phe-Cys]-OH
46	H-c[Cys-Phe-Phe-Trp-Lys-Thr-Phe-Cys]-OH
47	H-N(Me)-c[Cys-Lys-Phe-Phe- ^D Nal-Amp-Thr-Phe-Thr-Ser-Cys]-OH
48	H-N(Me)-c[Cys-Lys-Phe-Phe- ^D Trp-Amp-Thr-Phe-Thr-Ser-Cys]-OH
49	H-N(Me)-c[Cys-Lys-Phe-Phe- ^D Trp-Amp(NMe)-Thr-Phe-Thr-Ser-Cys]-OH
50	H-c[Cys-Lys-Phe-Phe- ^D Nal-Amp-Thr-Phe-Thr-Ser-Cys]-OH
51	H-c[Cys-Lys-Phe-Phe- ^D Trp-Lys-Thr-Tyr-Thr-Ser-Cys]-OH
52	H-c[Cys-Lys-Phe-Phe-Trp-3Pal-Thr-Tyr-Thr-Ser-Cys]-OH
53	H-c[Cys-Phe- ^D Trp-Lys-Thr-Phe-Cys]-OH
54	H-c[Cys-Phe-Phe- ^D Trp-Lys-Phe-Cys]-OH
55	H-c[Cys-Phe-Phe- ^D Trp-Lys-Thr-Cys]-OH
56	H-c[Cys-Phe-Phe- ^D Trp-Lys-Thr-Phe-Thr-Cys]-OH
57	H-c[Cys-Phe-Phe- ^D Trp-Lys-Thr-Phe-Thr-Cys]-OH
58	H-c[Cys-Lys-Phe-Phe- ^D Trp-3Pal-Thr-Phe-Cys]-OH
59	H-c[Cys-Lys-Phe-Phe- ^D Trp-Lys-Thr-Phe-Cys]-OH

60	H-c[Cys-Asn-Phe-Phe- ^D Trp-Lys-Thr-Phe-Cys]-OH
61	H-c[Cys-Asn-Phe-Phe- ^D Trp-Lys-Thr-Phe-Thr-Cys]-OH
62	H-Tyr-c[Cys-Phe- ^D Trp-Lys-Thr-Phe-Cys]-OH
63	H-Tyr-c[Cys-Lys-Phe- ^D Trp-3Pal-Thr-Phe-Thr-Cys]-OH
64	H-Tyr-c[Cys-Lys-Glu2-Phe- ^D Trp-3Pal-Thr-Phe-Lys2-Ser-Cys]-OH
65	H-Tyr-c[Cys-Lys-Phe-Glu2-Phe- ^D Trp-3Pal-Thr-Phe-Lys2-Ser-Cys]-OH
66	H-c[Cys-Phe-4Aph-Trp-Lys-Thr-Phe-Cys]-OH
67	H-c[Cys-Phe-4Aph- ^D Trp-Lys-Thr-Phe-Cys]-OH
68	H-N(Cbm)-c[Cys-Phe-4Aph-Trp-Lys-Thr-Phe-Cys]-OH
69	H-N(Cbm)-c[Cys-Phe-4Aph- ^D -Trp-Lys-Thr-Phe-Cys]-OH
70	H-c[Cys-Phe-4Aph-2Nal-Lys-Thr-Phe-Cys]-OH
71	H-Tyr-c[Cys-Phe-4Aph-Trp-Lys-Thr-Phe-Cys]-OH
72	H-Tyr-c[Cys-Phe-4Aph- ^D -Trp-Lys-Thr-Phe-Cys]-OH
73	H- N(Cbm)-Tyr-c[Cys-Phe-4Aph-Trp-Lys-Thr-Phe-Cys]-OH
74	H-c[Cys-Phe-4Aph-Trp-Lys-Thr-Tyr-Cys]-OH
75	H- N(Cbm)-c[Cys-Phe-4Aph-Trp-Lys-Thr-Tyr-Cys]-OH
76	H-c[Cys-Phe-Ala-Trp-Lys-Thr-Phe-Cys]-OH
77	H-Tyr-c[Cys-Phe-Ala-Trp-Lys-Thr-Phe-Cys]-OH
78	H-Tyr-c[Cys-Phe-Ala- ^D -Trp-Lys-Thr-Phe-Cys]-OH
79	H-Tyr-c[Cys-Phe-4Amp-Trp-Lys-Thr-Phe-Cys]-OH
80	H-c[^D Cys-Phe-Tyr-threo(2R,3S)C ^β Me-2Nal-Lys-Thr-Phe-Cys]-OH
81	H-c[Cys-Phe-Tyr-threo(2R,3S)C ^β Me-2Nal-Lys-Thr-Phe-Cys]-OH
82	H- N(Cbm)-c[Cys-Phe-4Aph- ^D -Trp-Lys-Thr-Tyr-Cys]-OH
83	H-c[Cys-Phe-Val- ^D Trp-Lys-Thr-Phe-Cys]-OH
84	H-c[Cys-Phe-Ala-Trp-Lys-Thr-Ala-Cys]-OH
85	H-c[Cys-Phe-Ala- ^D Trp-Lys-Thr-Ala-Cys]-OH
86	H-c[Cys-Phe-Ala-Trp-Lys-Thr-Phe-Cys]-OH
87	H-GABA-c[Cys-Phe-Ala-Trp-Lys-Thr-Phe-Cys]-OH
88	H-c[Cys-Phe-Ala-Trp-Lys-Thr-Val-Cys]-OH
89	H-c[Cys-Phe-Val-Trp-Lys-Thr-Val-Cys]-OH
90	H-c[Cys-Phe-Ala-Trp-Lys-Thr-Gly-Cys]-OH
91	H-Phe-c[Cys-Phe-Ala-Trp-Lys-Thr-Phe-Cys]-OH
92	H- N(Cbm)-Tyr-c[Cys-Phe-Ala-Trp-Lys-Thr-Phe-Cys]-OH
93	H- N(Cbm)-Tyr-c[Cys-Phe-Amp-Trp-Lys-Thr-Phe-Cys]-OH
94	H-Tyr-c[Cys-Phe-4Iamp-Trp-Lys-Thr-Phe-Cys]-OH
95	H-c[^D Cys-Phe-Tyr-threo(2S,3R)C ^β Me-2Nal-Lys-Thr-Phe-Cys]-OH
96	H-c[Cys-Phe-Tyr-threo(2S,3R)C ^β Me-2Nal-Lys-Thr-Phe-Cys]-OH

[157] Exemplary abbreviations and modifications in Table 4 are illustrated in FIG. 18A and FIG. 18B.

[158] The targeting ligands can comprise small molecule compounds. Such small molecule compounds can comprise L-797,591, L-779,976, L-796,778, L-803,087, or L-817,818, the structures of which are illustrated in FIG. 2A

[159] The targeting ligand can have a binding affinity to a human SSR that is not more than about 1mM, by half maximal inhibitory concentration (IC_{50}). The targeting ligand can have a binding affinity to a human SSR that is not more than about 1000nM, as measured by half maximal inhibitory concentration (IC_{50}). The targeting ligand can have a binding affinity to a human SSR that is not more than about 500nM, as measured by half maximal inhibitory concentration (IC_{50}). The targeting ligand can have a binding affinity to a human SSR that is not more than about 250nM, as measured by half maximal inhibitory concentration (IC_{50}). The targeting ligand can have a binding affinity to a human SSR that is not more than about 200nM, as measured by half maximal inhibitory concentration (IC_{50}). The targeting ligand can have a binding affinity to a human SSR that is not more than about 150nM, as measured by half maximal inhibitory concentration (IC_{50}). The targeting ligand can have a binding affinity to a human SSR that is not more than about 100nM, as measured by half maximal inhibitory concentration (IC_{50}). The targeting ligand can have a binding affinity to a human SSR that is not more than about 75nM, as measured by half maximal inhibitory concentration (IC_{50}). The targeting ligand can have a binding affinity to a human SSR that is not more than about 50nM, as measured by half maximal inhibitory concentration (IC_{50}). The targeting ligand can have a binding affinity to a human SSR that is not more than about 25nM, as measured by half maximal inhibitory concentration (IC_{50}). The targeting ligand can have a binding affinity to a human SSR that is not more than about 10nM, as measured by half maximal inhibitory concentration (IC_{50}). The targeting ligand can have a binding affinity to a human SSR that is not more than about 5nM, as measured by half maximal inhibitory concentration (IC_{50}). The targeting ligand can have a binding affinity to a human SSR that is not more than about 2nM, as measured by half maximal inhibitory concentration (IC_{50}). The targeting ligand can comprise a monocyclic peptide or peptide mimics or derivatives thereof.

Radionuclide

[160] In one aspect, described herein are conjugates that comprise a radionuclide. Exemplary radionuclides include, but are not limited to, astatine-211, astatine-217, actinium-225, americium-243, radium-223, lead-212, lead-203, copper-64, copper-67, copper-60, copper-61, copper-62, bismuth-212, bismuth-213, gallium-68, gallium-67, dysprosium-154, gadolinium-148, gadolinium-153, samarium-146, samarium-147, samarium-153, terbium-149, thorium-227, thorium-229, iron-59, yttrium-86, indium-111, holmium-166, technetium-94, technetium-99^m,

yttrium-90, lutetium-177, terbium-161, rhenium-186, rhenium-188, cobalt-55, scandium-43, scandium-44, scandium-47, dysprosium-166, fluorine-18, or iodine-131.

[161] Generally, the type of radionuclide used in a therapeutic radiopharmaceutical can be tailored to the specific type of cancer, the type of targeting moiety, etc. Radionuclides that undergo α -decay produce particles composed of two neutrons and two protons, and radionuclides that undergo β -decay emit energetic electrons from their nuclei. Some radionuclides can also emit Auger. In some embodiments, the conjugate comprises an alpha particle-emitting radionuclide. Alpha radiation can cause direct, irreparable double-strand DNA breaks compared with gamma and beta radiation, which can cause single-stranded breaks via indirect DNA damage. The range of these particles in tissue and the half-life of the radionuclide can also be considered in designing the radiopharmaceutical conjugate. Tables 5A and 5B below illustrate some properties of exemplary radionuclides.

Table 5A. Exemplary radionuclides

Radionuclide	Emission	Half-life (days)
Copper-67	β	about 2.6
Rhodium-105	β	about 1.5
Indium-111	β	about 2.8
Actinium-225 (Ac-225)	α	about 10.0
Lutetium (Lu-177)	β	about 6.7
Radium-223	α	about 11.4
Radium-224	α	about 3.63
Astatine-211	α	about 0.3
Yttrium-90	β	about 2.7
Gadolinium-148	α	about 74
Samarium-153	β	about 1.9
Promethium-153	β	about 5.25 min.
Thulium-167	β	about 9.3
Ytterbium-175	β	about 4.2
Lead-212	β	about 0.4
Bismuth-209	α	stable
Bismuth-212	α	about 0.04
Bismuth-213	α	about 0.03
Polonium-213	α	about 4.2 μ sec.
Francium-223	α	about 0.015
Thorium-227	α	about 18.7
Thorium-229	α	about 7.3
Terbium-149	α	about 0.17

Table 5B. Exemplary radionuclides

Nuclide	Half-life
Lutetium-177 (Lu-177)	about 6.6 days
Indium-111 (In-111)	about 2.8 days
Gallium-68 (Ga-68)	about 68 minutes
Copper-62 (Cu-62)	about 9.6 minutes
Copper-64 (Cu-64)	about 12.7 hours
Zirconium-89 (Zr-89)	about 78.4 hours
Technetium-99m	about 6 hours
Cerium-134 (Ce-134)	about 3.2 days
Terbium-152	about 17.5 hours

[162] In some embodiments, a conjugate described herein comprises one or more independent radionuclides. In some embodiments, the conjugate comprises two radionuclides. In some embodiments, each of the one or more radionuclides is bound to a metal chelator of the conjugate. In some embodiments, two radionuclides of a conjugate are bound to the same metal chelator. In some embodiments, two radionuclides of a conjugate are bound to two independent metal chelators. In some embodiments, each of the one or more radionuclides is an alpha particle-emitting radionuclide.

[163] In some embodiments, a conjugate described herein comprises an alpha particle-emitting radionuclide. In some embodiments, the alpha particle-emitting radionuclide is actinium-225 (^{225}Ac), astatine-211 (^{211}At), radium-223 (^{223}Ra), radium-224 (^{224}Ra), bismuth-213 (^{213}Bi), Terbium-149 (^{149}Tb), or thorium-227 (^{227}Th). In some embodiments, the alpha particle-emitting radionuclide is ^{225}Ac . In some embodiments, the alpha particle-emitting radionuclide is ^{213}Bi . In some embodiments, the alpha particle-emitting radionuclide is ^{212}Bi . In some embodiments, the alpha particle-emitting radionuclide is ^{212}Pb . In some embodiments, the alpha particle-emitting radionuclide is ^{224}Ra . In some embodiments, the alpha particle-emitting radionuclide is ^{223}Ra . In some embodiments, the alpha particle-emitting radionuclide is ^{227}Th . In some embodiments, the alpha particle-emitting radionuclide is ^{211}At . In some embodiments, the alpha particle-emitting radionuclide is ^{149}Tb . In some embodiments, the radionuclide is Zirconium-89 (^{89}Zr). In some embodiments, a conjugate described herein comprises a radionuclide selected from ^{67}Cu , ^{64}Cu , ^{89}Zr , ^{90}Y , ^{109}Pd , ^{111}Ag , ^{149}Pm , ^{153}Sm , ^{166}Ho , $^{99\text{m}}\text{Tc}$, ^{67}Ga , ^{68}Ga , ^{111}In , ^{90}Y , ^{177}Lu , ^{186}Re , ^{188}Re , ^{197}Au , ^{198}Au , ^{199}Au , ^{105}Rh , ^{165}Ho , ^{161}Tb , ^{149}Pm , ^{44}Sc , ^{47}Sc , ^{70}As , ^{71}As , ^{72}As , ^{73}As , ^{74}As , ^{76}As , ^{77}As , ^{212}Pb , ^{212}Bi , ^{213}Bi , ^{225}Ac , $^{117\text{m}}\text{Sn}$, ^{67}Ga , ^{201}Tl , ^{123}I , ^{131}I , ^{160}Gd , ^{148}Nd , ^{89}Sr , and ^{211}At . In some embodiments, the radionuclide is ^{225}Ac . In some embodiments, the radionuclide is a decay daughter of ^{225}Ac such as ^{221}Fr , ^{217}At , ^{213}Bi , ^{213}Po , ^{209}Tl , ^{209}Pb , or ^{209}Bi . In some embodiments, the conjugate comprises two ^{225}Ac radionuclides. In some embodiments, the radionuclide is ^{177}Lu . In some embodiments, the radionuclide is no-carrier added (i.e., non-carrier-added or n.c.a.) ^{177}Lu .

In some embodiments, the radionuclide is no-carrier added (i.e., non-carrier-added or n.c.a.) ^{225}Ac . In some embodiments, the radionuclide is ^{177}Lu free of long-lived radioactive contaminants and byproducts. In some embodiments, the conjugate comprises two ^{177}Lu radionuclides. In some embodiments, the radionuclide is a non-carrier-added radionuclide.

[164] In some embodiments, the alpha particle-emitting radionuclide is ^{225}Ac . In some embodiments, the alpha particle-emitting radionuclide is no-carrier added (i.e., non-carrier-added or n.c.a.) ^{225}Ac . In some embodiments, the ^{225}Ac is free of long-lived radioactive contaminants and byproducts. In some embodiments, the alpha particle-emitting radionuclide is carrier added ^{225}Ac . In some embodiments, ^{225}Ac is generated from a heavier radionuclide. In some embodiments, ^{225}Ac is generated using a Thorium-229 generator. In some embodiments, ^{225}Ac is generated via ^{229}Th decay to ^{225}Ra from which ^{225}Ra and ^{225}Ac are then separated via ionic exchange resins. In some embodiments, ^{229}Th is generated by legacy ^{233}U stock provided by government sources. In some embodiments, ^{225}Ac is generated using Electron Linear Accelerators (LINAC) with radium-226 as a target source. In some embodiments, ^{225}Ac is generated by the $^{226}\text{Ra}(\gamma, n)^{225}\text{Ra}$ reaction using an electron linear accelerator, and subsequent separation and purification of ^{225}Ra and ^{225}Ac using a series of ionic exchange resins. In some embodiments, ^{225}Ac is generated using a cyclical proton accelerator using radium-226 as a target source. In some embodiments, ^{225}Ac is generated by the $^{226}\text{Ra}(p, 2n)^{225}\text{Ac}$ reaction using a low energy cyclical proton accelerator (aka cyclotron). In some embodiments, ^{225}Ac is generated by the $^{226}\text{Ra}(p, 2n)^{225}\text{Ac}$ reaction using a low energy cyclical proton accelerator (aka cyclotron) having an energy range between 10-20 MeV. In some embodiments, ^{225}Ac is generated using electron beam accelerators (rhodotron) using radium-226 as a target source. In some embodiments, ^{225}Ac is generated by the $^{226}\text{Ra}(\gamma, n)^{225}\text{Ra}$ reaction using an electron beam accelerator, and subsequent separation and purification of ^{225}Ra and ^{225}Ac using a series of ionic exchange resins. In some embodiments, ^{225}Ac is generated using high energy proton spallation using thorium-232 as a target source. In some embodiments, ^{225}Ac is generated using by the $^{232}\text{Th}(p, npx)^{225}\text{Ac}$ reaction using a 70-100 MeV+ high energy proton accelerator.

[165] In some embodiments, the conjugate comprises an alpha particle-emitting radionuclide bound to the metal chelator. In some embodiments, the alpha particle-emitting radionuclide is actinium-225, astatine-211, thorium-227, or radium-223. In some embodiments, the alpha particle-emitting radionuclide is actinium-225.

[166] In some embodiments, the conjugate comprises a beta particle-emitting radionuclide bound to the metal chelator. In some embodiments, the beta particle emitting radionuclide is zirconium-89, yttrium-90, iodine-131, samarium-153, lutetium-177, or lead-212.

[167] In some embodiments, the conjugate comprises a gamma particle emitting radionuclide. In some embodiments, the gamma particle emitting radionuclide is indium-111.

[168] In some embodiments, conjugates described herein do not contain any radionuclide, i.e., a cold conjugate. For example, in some cases, a radionuclide can be replaced with a surrogate (e.g., ²²⁵Ac replaced with lanthanum) for testing and experimental purposes.

Metal Chelator

[169] In one aspect, described herein are conjugates that comprise a metal chelator that is configured to bind with a radionuclide. The metal chelator can refer to a moiety of the conjugate that is configured to bind with a radionuclide. In some embodiments, a conjugate described herein comprises two or more independent metal chelators, e.g., 2, 3, 4, 5, or more metal chelators. In some embodiments, a conjugate described herein comprises two metal chelators, which can be the same or different. The metal chelator can be attached to the linker or the targeting ligand through any suitable group/atom of the chelator.

[170] In some embodiments, the metal chelator is capable of binding a radioactive atom. The binding can be direct, e.g., the metal chelator can make hydrogen bonds or electrostatic interactions with the radioactive atom. The binding can also be indirect, e.g., the metal chelator binds to a molecule that comprises a radioactive atom. In some embodiments, the metal chelator comprises, or is, a macrocycle. In some embodiments, the metal chelator comprises, or is, DOTA or NOTA. In some embodiments, the metal chelator comprises a macrocycle, e.g., a macrocycle comprising an O and/or an N atom, DOTA, NOTA, one or more amines, one or more ethers, one or more carboxylic acids, EDTA, DTPA, TETA, DO3A, PCTA, or desferrioxamine.

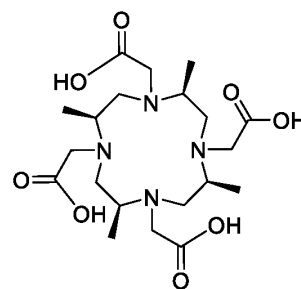
[171] In some embodiments, the metal chelator comprises a plurality of amines. In some embodiments, the metal chelator includes 4 or more N atoms, 4 or more carboxylic acid groups, or a combination thereof. In some embodiments, the metal chelator does not comprise an S atom. In some embodiments, the metal chelator comprises a ring. In some embodiments, the ring comprises an O and/or an N atom. In some embodiments, the metal chelator is a ring that includes 3 or more N atoms, 3 or more carboxylic acid groups, or a combination thereof. In some embodiments, the metal chelator is poly polydentate.

[172] In some embodiments, a metal chelator described herein comprises a cyclic chelating agent. Exemplary cyclic chelating agents include, but are not limited to, AAZTA, BAT, BAT-TM, Crown, Cyclen, DO2A, CB-DO2A, DO3A, H3HP-DO3A, Oxo-DO3A, p-NH₂-Bn-Oxo-DO3A, DOTA, DOTA-3py, DOTA-PA, DOTA-GA, DOTA-4AMP, DOTA-2py, DOTA-1py, p-SCN-Bn-DOTA, CHX-A"-EDTA, MeO-DOTA-NCS EDTA, DOTAMAP, DOTAGA, DOTAGA-anhydride, DOTMA, DOTASA, DOTAM, DOTP, CB-Cyclam, TE2A, CB-TE2A, CB-TE2P, DM-TE2A, MM-TE2A, NOTA, NOTP, HEHA, HEHA-NCS, p-SCN-Bn-HEHA,

DTPA, CHX-A''-DTPA, p-NH₂-Bn-CHX-A''-DTPA, p-SCN-DTPA, p-SCN-Bz-Mx-DTPA, 1B4M-DTPA, p-SCN-Bn1B-DTPA, p-SCN-Bn-1B4M-DTPA, p-SCN-Bn-CHX-A''-DTPA, PEPA, p-SCN-Bn-PEPA, TETPA, DOTPA, DOTMP, DOTPM, t-Bu-calix[4]arene-tetracarboxylic acid, macropa, macropa-NCS, macropid, H₃L¹, H₃L⁴, H₂azapa, H₅decapa, bispa², H₄pypa, H₄octapa, H₄CHXoctapa, p-SCN-Bn-H₄octapa, p-SCN-Bn-H₄octapa, TTHA, p-NO₂-Bn-neunpa, H₄octox, H₂macropa, H₂bispa², H₄phospa, H₆phospa, p-SCN-Bn-H₆phospa, TETA, p-NO₂-Bn-TETA, TRAP, TPA, HBED, SHBED, HBED-CC, (HBED-CC)TFP, DMSA, DMPS, DHLA, lipoic acid, TGA, BAL, Bis-thioseminarabazones, p-SCN-NOTA, nNOTA, NODAGA, CB-TE1A1P, 3P-C-NETA-NCS, 3p-C-DEPA, 3P-C-DEPA-NCS, TCMC, PCTA, NODIA-Me, TACN, pycup1A1B, pycup2A, THP, DEDPA, H₂DEDPA, p-SCN-Bn-H₂DEDPA, p-SCN-Bn-TCMC, motexafin, NTA, NOC, 3p-C-NETA, p-NH₂-Bn-TE3A, SarAr, DiAmSar, SarAr-NCS, AmBaSar, BaBaSar, TACN-TM, CP256, C-NE3TA, C-NE3TA-NCS, NODASA, NETA-monoamide, C-NETA, NOPO, BPCA, p-SCN-Bn-DFO, DFO-ChX-Mal, DFO, DFO-IAC, DFO-BAC, DiP-LICAM, EC, SBAD, BAPEN, TACHPYR, NEC-SP, L^{py}, L1, L2, L3, and EuK-106.

[173] In some embodiments, the metal chelator is DO3A. In some embodiments, the metal chelator is PEPA. In some embodiments, the metal chelator is EDTA. In some embodiments, the metal chelator is CHX-A''-DTPA. In some embodiments, the metal chelator is HEHA. In some embodiments, the metal chelator is DOTMP. In some embodiments, the metal chelator is t-Bu-calix[4]arene-tetracarboxylic acid. In some embodiments, the metal chelator is macropa. In some embodiments, the metal chelator is macropa-NCS. In some embodiments, the metal chelator is H⁴py4pa. In some embodiments, the metal chelator is H₄octapa. In some embodiments, the metal chelator is H₄CHXoctapa. In some embodiments, the metal chelator is DOTP. In some embodiments, the metal chelator is crown.

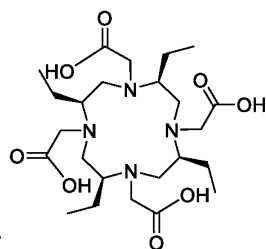
[174] In some embodiments, the metal chelator is DOTA. In some embodiments, the metal chelator is a chiral derivative of DOTA. In some embodiments, the metal chelator is DOTA-GA. Exemplary chiral DOTA chelators are described in Dai et al., Nature Communications (2018) 9:857. In some embodiments, the metal chelator is 2,2',2'',2'''-((2S,5S,8S,11S)-2,5,8,11-tetramethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl)tetraacetic acid. In some



embodiments, the metal chelator has a structure of

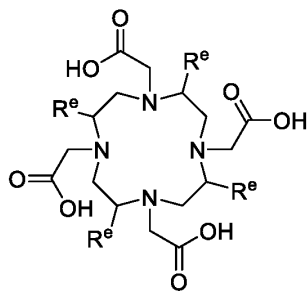
. In some

embodiments, the metal chelator is 2,2',2'',2'''-((2S,5S,8S,11S)-2,5,8,11-tetraethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl)tetraacetic acid. In some embodiments, the metal chelator



has a structure of

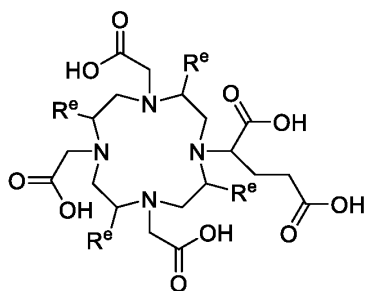
. In some embodiments of a conjugate described herein,



the metal chelator has a structure of

, wherein each R^e is independently

selected from hydrogen, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocycloalkyl, alkylaryl, alkylheteroaryl, or an amino acid side chain. In some embodiments, the metal chelator has a



structure of

wherein each R^e is independently selected from

hydrogen, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocycloalkyl, alkylaryl, alkylheteroaryl, or an amino acid side chain.

[175] In some embodiments, the conjugate comprises DOTA. In some embodiments, the conjugate comprises a DOTA derivative such as p-SCN-Bn-DOTA and MeO-DOTA-NCS. In some embodiments, the conjugate comprises two independent metal chelators, and at least one or both are DOTA. The structures of some exemplary metal chelators are illustrated in FIGs. 3-17 (without showing the attachment points). Exemplary metal chelators are further described in WO2012/174136; US20130183235A1; US20120219495A1; Ramogidaand et al., EJNMMI radiopharm. chem. 4, 21 (2019); Thiele et al., Cancer Biotherapy and Radiopharmaceuticals 2018;

Li et al., *Bioconjugate Chem.* 2019, 30, 5, 1539–1553; and Baranyai et al., *Eur. J. Inorg. Chem.* 36–56 (2020), each of which is incorporated by reference in its entirety.

Linker

[176] A chemical scaffold, covalently joining pharmacophore and metal-chelator in a targeted radiopharmaceutical, can be referred to as a linker. Incorporating a well-designed linker to a drug molecule can further boost affinity towards its biological target, accelerate internalization into the targeted tissues, and optimize the pharmacokinetic properties. Diverse chemical moieties can be used to construct the linkers. By changing their physio-chemical characters, the desired in vivo characters (i.e. absorption, distribution, metabolism, and excretion of the drug molecules) can be achieved. In some embodiments, physio-chemical characters of the conjugates can be adjusted by the linkers, for example, when it is difficult to change pharmacophore and metal-chelating portions without sacrificing the biological affinity or metal-binding ability. A conjugate described herein can comprise one or more linkers. The targeting ligand can be covalently linked to the metal chelator through a linker. The linker can covalently attach the targeting ligand with the metal chelator. The targeting ligand can also attach directly to the metal chelator without a linker.

[177] A linker can comprise one or more amino acid residues. The linker can comprise 1 to 3, 1 to 5, 1 to 10, 5 to 10, or 5 to 20 amino acid residues. The linker can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid residues. The linker can comprise 1 to 5 amino acid residues. For example, the linker can comprise one or more lysine (K) residues such as K, KK, or KKK sequences. The linker can comprise a lysine or a derivative thereof. The linker can comprise a lysine. The linker can comprise one or more amino acids that are unnatural amino acids.

[178] A herein-described linker can attach to the N-terminus of the peptide, the C-terminus of the peptide, or a non-terminal amino acid of the peptide, or it can attach to the peptide through a combination of the above. In some embodiments, the linker is attached to the peptide via its N-terminus. In some embodiments, the linker is attached to the peptide via its C-terminus. In some embodiments, the linker is attached to the peptide via a non-terminal amino acid. The linker can be bonded to the peptide, the metal chelator, or both, for example, through a chemically reactive group. Exemplary chemically reactive groups include, but are not limited to, a free amino, imino, hydroxyl, thiol or carboxyl group (e.g., to the N- or C-terminus, to the epsilon amino group of one or more lysine residues, the free carboxylic acid group of one or more glutamic acid or aspartic acid residues, or to the sulfhydryl group of one or more cysteinyl residues). The site to which the linker is bound to the peptide can be a natural or unnatural amino acid of the peptide and/or it can be introduced into the peptide, e.g., by DNA recombinant technology (e.g., by introducing a cysteine or protease cleavage site in the amino acid sequence) or by protein biochemistry (e.g., reduction, pH adjustment or proteolysis). Exemplary methods for attaching the linker includes

carbodiimide reaction, reactions using bifunctional agents such as dialdehydes or imidoesters, Schiff base reaction, Suzuki-Miyaura cross-coupling reactions, Isothiocyanates as coupling agents, and click chemistry.

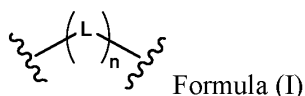
[179] The linker can have a prescribed length thereby linking the metal chelator (and optionally radionuclide) and the peptide while allowing an appropriate distance therebetween. In some embodiments, the linker has 1 to 100 atoms, 1 to 60 atoms, 1 to 30 atoms, 1 to 15 atoms, 1 to 10 atoms, 1 to 5, or 2 to 20 atoms in length. In some embodiments, the linker has 1 to 10 atoms in length.

[180] The linker can comprise flexible and/or rigid regions. Exemplary flexible linker regions include those comprising Gly and Ser residues ("GS" linker), glycine residues, alkylene chain, PEG chain, etc. Exemplary rigid linker regions include those comprising alpha helix-forming sequences (e.g., EAAAK (SEQ ID NO: 104)), proline-rich sequences, and regions rich in double and/or triple bonds.

[181] In some embodiments, the linker comprises a click chemistry residue. The linker can be attached to the peptide, to the metal chelator, or both via click chemistry, thereby forming a click chemistry residue. For example, the peptide can comprise an azide group (at N- or C-terminus or at a non-terminal amino acid) that reacts with an alkyne moiety of the linker. For another example, the peptide can comprise an alkyne group (at N- or C-terminus or at a non-terminal amino acid) that reacts with an azide of the linker. The metal chelator and the linker can be attached similarly. In some embodiments, the linker comprises an azide moiety, an alkyne moiety, or both.

[182] A linker described herein can comprise one or more motifs. One or more of the motifs can be connected via click chemistry such that they can be clicked in/out of the linker. Each of the motifs in a linker can have independent functions. For example, a linker can comprise a motif that functions to adjust plasma half-life and/or a motif that functions as a spacer between the peptide and metal chelator.

[183] In some embodiments, the linker has a structure of



wherein each L is independently -O-, -NR^L-, -N(R^L)₂⁺-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, -S(=O)₂-, =CH-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -NR^LC(=S)NR^L-, -CR^L=N-, -N=CR^L-, -NR^LS(=O)₂-, -S(=O)₂NR^L-, -C(=O)NR^LS(=O)₂-, -S(=O)₂NR^LC(=O)-, substituted or unsubstituted C₁-C₃₀ alkylene, substituted or unsubstituted C₂-C₃₀ alkenylene, substituted or unsubstituted C₂-C₃₀ alkynylene, substituted or unsubstituted C₁-C₃₀ heteroalkylene, -(C₁-C₃₀ alkylene)-O-, -O-(C₁-C₃₀

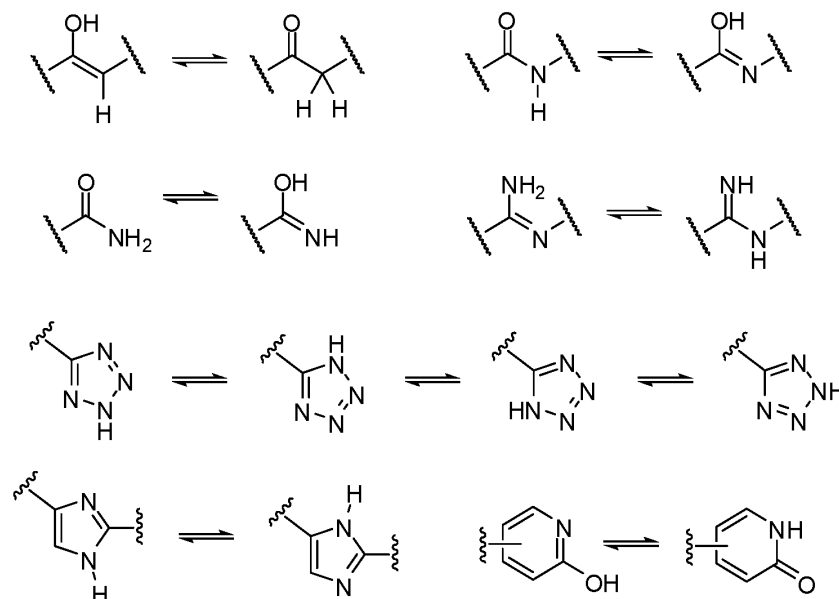
alkylene)-, -(C₁-C₃₀ alkylene)-NR^L-, -NR^L-(C₁-C₃₀ alkylene)-, -(C₁-C₃₀ alkylene)-N(R^L)₂⁺-, -N(R^L)₂⁺-(C₁-C₃₀ alkylene)-, or a click chemistry residue; and each R^L is independently hydrogen, substituted or unsubstituted C₁-C₄ alkyl, substituted or unsubstituted C₁-C₄ heteroalkyl, substituted or unsubstituted C₂-C₆ alkenyl, substituted or unsubstituted C₂-C₅ alkynyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted C₂-C₇ heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15.

Isomers/Stereoisomers

[184] In some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds presented herein include cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the corresponding mixtures thereof. In some situations, the compounds described herein possess one or more chiral centers and each center exists in the R configuration or S configuration. The compounds described herein include diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are useful for the applications described herein. In some embodiments, the compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers, and recovering the optically pure enantiomers. In some embodiments, dissociable complexes are preferred. In some embodiments, the diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent.

Tautomers

[185] A "tautomer" refers to a molecule wherein a proton shift from one atom of a molecule to another atom of the same molecule is possible. The compounds presented herein, in certain embodiments, exist as tautomers. In circumstances where tautomerization is possible, a chemical equilibrium of the tautomers will exist. The exact ratio of the tautomers depends on several factors, including physical state, temperature, solvent, and pH. Some examples of tautomeric equilibrium include:



[186] In some instances, the compounds disclosed herein exist in tautomeric forms. The structures of said compounds are illustrated in the one tautomeric form for clarity. The alternative tautomeric forms are expressly included in this disclosure.

Labeled compounds.

[187] In some embodiments, the compounds described herein exist in their isotopically-labeled forms. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds as pharmaceutical compositions. Thus, in some embodiments, the compounds disclosed herein include isotopically-labeled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds described herein, or a solvate, or stereoisomer thereof, include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, and chloride, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Compounds described herein, and the pharmaceutically acceptable salts, solvates, or stereoisomers thereof which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this disclosure. Certain isotopically-labeled compounds, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H and carbon-14, i.e., ^{14}C , isotopes are notable for their ease of preparation and detectability. Further, substitution with heavy isotopes such as deuterium, i.e., ^2H , produces certain therapeutic

advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements. In some embodiments, the isotopically labeled compound or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof is prepared by any suitable method.

[188] In some embodiments, the compounds described herein are labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

Pharmaceutically acceptable salts.

[189] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the compounds disclosed herein include their pharmaceutically acceptable salts. As used herein, a “pharmaceutically acceptable salt” refers to any salt of a stabilizing agent that is useful for stabilizing the radiopharmaceutical compositions. As used herein, a “pharmaceutically acceptable salt” refers to any salt of a stabilizing agent that is useful for preventing or delaying the decomposition of the radiopharmaceutical within the compositions.

[190] In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared *in situ* during the final isolation and purification of the compounds disclosed herein, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

[191] Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral acid, organic acid, or inorganic base, such salts including acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, bisulfite, bromide, butyrate, butyn-1,4-dioate, camphorate, camphorsulfonate, caproate, caprylate, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hexyne-1,6-dioate, hydroxybenzoate, γ -hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate, metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, 1-naphthalenesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, phthalate, phenylacetate, phenylbutyrate,

propanesulfonate, salicylate, succinate, sulfate, sulfite, succinate, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylate, undeconate, and xylenesulfonate.

[192] Further, the compounds described herein can be prepared as pharmaceutically acceptable salts formed by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, p-toluenesulfonic acid, tartaric acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, arylsulfonic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, and muconic acid.

[193] In some embodiments, the compounds described herein which comprise a free acid group react with a suitable base, such as the hydroxide, carbonate, bicarbonate, or sulfate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, tertiary, or quaternary amine. Representative salts include the alkali or alkaline earth salts, like lithium, sodium, potassium, calcium, and magnesium, and aluminum salts, and the like. Illustrative examples of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, $N^+(C_{1-4} \text{ alkyl})_4$, and the like.

[194] Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, and the like. It should be understood that the compounds described herein also include the quaternization of any basic nitrogen-containing groups they contain. In some embodiments, water or oil-soluble or dispersible products are obtained by such quaternization.

Solvates.

[195] In some embodiments, the compounds described herein exist as solvates. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and, in some embodiments, are formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of the compounds described herein can be conveniently prepared or formed during the processes described herein. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the

solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein. Accordingly, one aspect of the present disclosure pertains to hydrates and solvates of compounds of the present disclosure and/or their pharmaceutical acceptable salts, as described herein, that can be isolated and characterized by methods known in the art, such as, thermogravimetric analysis (TGA), TGA-mass spectroscopy, TGA-Infrared spectroscopy, powder X-ray diffraction (PXRD), Karl Fisher titration, high resolution X-ray diffraction, and the like.

Preparation of the Compositions

[196] The disclosure provides methods of preparing and making the compositions described herein. In some embodiments, the method of making the radiopharmaceutical composition comprises combining a radionuclide (such as ^{225}Ac) with an un-labeled conjugate (e.g., DOTATATE or DOTATOC) in the presence of one or more stabilizer agents, wherein the un-labeled conjugate comprises a targeting ligand and a metal chelator covalently attached to the targeting ligand, thereby producing a mixture comprising a labeled conjugate (e.g., ^{225}Ac -DOTATATE or ^{225}Ac -DOTATOC), and optionally combining one or more stabilizing agents to the mixture. In some embodiments, the method of making the radiopharmaceutical composition comprises combining a radionuclide with an un-labeled conjugate, wherein the un-labeled conjugate comprises a targeting ligand and a metal chelator covalently attached to the targeting ligand, thereby producing a labeled conjugate, and combining the one or more stabilizing agents with the labeled conjugate.

[197] In some embodiments, the method of making the radiopharmaceutical composition comprises combining a radionuclide with an un-labeled conjugate, which comprises a targeting ligand and a metal chelator covalently attached to the targeting ligand, thereby producing a labeled conjugate, and adding the one or more stabilizing agents to the labeled conjugate. In some embodiments, the method of making the radiopharmaceutical composition comprises combining a radionuclide with an un-labeled conjugate which comprises a targeting ligand and a metal chelator covalently attached to the targeting ligand, in the presence of one or more stabilizer agents, thereby producing a labeled conjugate, and optionally adding one or more stabilizing agents to the labeled conjugate.

[198] The method of making the compositions can comprise one or multiple steps. One or more such steps can comprise diluting a radionuclide-containing solution or mixture to a desired concentration (i.e., a dilution step). The radionuclide-containing solution or mixture can be diluted by 2 to 1000 fold, e.g., 10-50 fold, 2-40 fold, 25-75 fold, or 50-100 fold. One or more such steps can comprise adding one or more stabilizing agents during the process of dilution. One or more such steps can comprise optionally adding one or more stabilizing agents during the process of

dilution. One or more such steps can comprise diluting an un-labeled conjugate solution or mixture to a desired concentration. One or more such steps can comprise adding one or more stabilizing agents before the process of dilution. One or more such steps can comprise adding one or more stabilizing agents after the process of dilution. The un-labeled conjugate can comprise a targeting ligand and a metal chelator. The targeting ligand and the metal chelator can be linked covalently. One or more such steps can comprise dilution using a liquid solution or mixture.

[199] A method of making a radiopharmaceutical composition can comprise reacting or combining a radionuclide with an un-labeled conjugate solution or mixture to obtain a labeled conjugate solution or mixture (i.e., a labeling process). In some embodiments, the method comprises maintaining a temperature during the labeling process. In some embodiments, the method comprises maintaining a temperature ranging from 0°C to 100°C, from 10°C to 100°C, from 20°C to 100°C, from 30°C to 100°C, from 40°C to 100°C, from 50°C to 100°C, from 60°C to 100°C, from 70°C to 100°C, or from 80°C to 100°C. In some embodiments, the method comprises reacting the radionuclide with the un-labeled conjugate for a period of time. In some embodiments, the period of time is from about 1 minute to about 3 hours, from about 2 minutes to about 2.5 hours, from about 3 minutes to about 2 hours, from about 5 minutes to about 1.5 hours, from about 8 minutes to about 1 hours, or from about 10 minutes to about 30 minutes. In some embodiments, the method comprises mixing the radionuclide with the un-labeled conjugate during the labeling process. One or more such steps can comprise mixing using laboratory mixing equipment such as a mixer, a vortex mixer, a stirrer, a magnetic stirrer, a spinner, a shaker, a centrifuge, or a homogenizer. One or more such steps can comprise shaking the reaction solution or mixture. One or more such steps can comprise shaking the reaction solution or mixture at a speed ranging from about 10 rpm to about 5000 rpm, from about 100 rpm to about 2500 rpm, from about 200 rpm to about 1000 rpm, from about 300 rpm to about 800 rpm, or from about 400 rpm to about 600 rpm. One or more such steps can comprise further diluting the labeled conjugate solution or mixture. One or more such steps can comprise adding one or more stabilizing agents during the process of dilution. One or more such steps can comprise optionally adding one or more stabilizing agents after the process of dilution.

[200] In some embodiments, a radiopharmaceutical composition comprising [²²⁵Ac]Ac-DOTA-TATE (or ²²⁵Ac-DOTA-TATE) can be prepared by reacting DOTA-TATE with [²²⁵Ac]AcCl₃ from HCl (e.g., 0.04M, aqueous) solution. Accordingly, provide herein are methods of making a radiopharmaceutical composition comprising ²²⁵Ac-DOTA-TATE. In some embodiments, the method comprises one or more of the following steps: diluting DOTA-TATE with sodium acetate/acetic acid buffer solution, adding [²²⁵Ac]AcCl₃ HCl solution to the diluted DOTA-TATE, mixing the mixture, heating the mixture, and diluting into a formulation buffer

with one or more stabilizing agents described herein. In some embodiments, the concentration of $[^{225}\text{Ac}]\text{AcCl}_3$ in the HCl solution is about 10 $\mu\text{Ci}/\mu\text{l}$ HCl. In some embodiments, the concentration of $[^{225}\text{Ac}]\text{AcCl}_3$ in the HCl solution is about 1 to 50 $\mu\text{Ci}/\mu\text{l}$ HCl. A radiopharmaceutical composition comprising ^{225}Ac -HA-DOTA-TATE or ^{225}Ac -DOTA-JR-11 can be prepared accordingly.

[201] In some embodiments, a method of making a radiopharmaceutical composition comprising $[^{225}\text{Ac}]\text{Ac}$ -DOTA-TATE or $[^{225}\text{Ac}]\text{Ac}$ -DOTA-TOC comprises one or more of the following steps: providing $[^{225}\text{Ac}]\text{AcCl}_3$ solution in a first vial, transferring such solution into a reactor, providing a reaction buffer solution into the first vial containing $[^{225}\text{Ac}]\text{AcCl}_3$ solution, transferring the reaction buffer solution and residual $[^{225}\text{Ac}]\text{AcCl}_3$ solution from the first vial to the reactor, transferring a DOTA-TATE or a DOTA-TOC solution into the reactor, reacting the DOTA-TATE or DOTA-TOC solution with $[^{225}\text{Ac}]\text{AcCl}_3$ solution in the reactor to obtain $[^{225}\text{Ac}]\text{Ac}$ -DOTA-TATE or $[^{225}\text{Ac}]\text{Ac}$ -DOTA-TOC, and diluting the $[^{225}\text{Ac}]\text{Ac}$ -DOTA-TATE or $[^{225}\text{Ac}]\text{Ac}$ -DOTA-TOC in a formulation buffer comprising one or more stabilizing agents described herein to form the radiopharmaceutical composition. In some embodiments, the molar ratio of ^{225}Ac to DOTA-TATE or DOTA-TOC is from 1:1 to 1:10, from 1:1 to 1:8, from 1:1 to 1:5, from 1:1 to 1:3.5, from 1:1 to 1:2, or from 1:1 to 1:25. In some embodiments, the molar ratio of ^{225}Ac to DOTA-TATE or DOTA-TOC is about 1:1, 1:2, 1:25, 1:3, 1:3.5 or 1:4. A radiopharmaceutical composition comprising ^{225}Ac -HA-DOTA-TATE or ^{225}Ac -DOTA-JR-11 can be prepared accordingly.

[202] The compounds used in the reactions and compositions described herein are made according to organic synthesis techniques known to those skilled in this art, starting from commercially available chemicals and/or from compounds described in the chemical literature. "Commercially available chemicals" are obtained from standard commercial sources including ABX advanced biochemical compounds GmbH (Radeberg, Germany), Acros Organics (Pittsburgh, PA), Aldrich Chemical (Milwaukee, WI, including Sigma Chemical and Fluka), Apin Chemicals Ltd. (Milton Park, UK), 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, NY), Eastman Organic Chemicals, Eastman Kodak Company (Rochester, NY), Fisher Scientific Co. (Pittsburgh, PA), Fisons Chemicals (Leicestershire, UK), Frontier Scientific (Logan, UT), ICN Biomedicals, Inc. (Costa Mesa, CA), ITM (Munich, Germany), Key Organics (Cornwall, U.K.), Lancaster Synthesis (Windham, NH), Maybridge Chemical Co. Ltd. (Cornwall, U.K.), Parish Chemical Co. (Orem, UT), Pfaltz & Bauer, Inc. (Waterbury, CN), Polyorganix (Houston, TX), Pierce Chemical Co. (Rockford, IL), Riedel de Haen AG (Hanover, Germany), Sigma-Aldrich (U.S.A.), Spectrum Quality Product, Inc. (New

Brunswick, NJ), TCI America (Portland, OR), Trans World Chemicals, Inc. (Rockville, MD), VWR (Radnor, PA, USA), Wako Chemicals USA, Inc. (Richmond, VA), and Wuxi-Apptech Inc. (Shanghai, China).

Method of Treatment

[203] In one aspect, the disclosure provides methods of treating a disease or condition in a subject in need thereof. The methods can comprise administering a radiopharmaceutical composition to the subject in need thereof. The methods can provide a therapeutic and/or prophylactic benefit to a subject in need thereof comprising administering a radiopharmaceutical composition described herein.

[204] The methods can comprise administering to a subject a radiopharmaceutical composition that comprise a therapeutically effective amount of a conjugate or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the subject has cancer. In some embodiments, the cancer is a solid tumor. In some embodiments, the cancer is an SSR-associated cancer. In some embodiments, the cancer is an SSTR2-associated cancer. In some embodiments, the cancer is a somatostatin receptor-positive (SSTR+) cancer.

[205] In some embodiments, the cancer is a neuroendocrine cancer, a lymphatic cancer, a pancreatic cancer, a pituitary cancer, a breast cancer, a lung cancer, a stomach cancer, medulloblastoma, or neuroblastoma. In some embodiments, the cancer is a neuroendocrine cancer. In some embodiments, the neuroendocrine cancer is recurrent or refractory. In some embodiments, the neuroendocrine cancer is refractory to a radiotherapy that comprises beta-particle emitting radionuclide (such as ^{177}Lu -DOTA-TATE or ^{177}Lu -DOTA-TOC therapy). In some embodiments, the subject has received a radiotherapy that comprises beta-particle emitting radionuclide prior to the administering of the radiopharmaceutical composition (such as ^{177}Lu -DOTA-TATE or ^{177}Lu -DOTA-TOC therapy). In some embodiments, the subject has received a prior treatment of ^{177}Lu -DOTA-TATE. In some embodiments, the subject has received a prior treatment of ^{177}Lu -DOTA-TOC therapy. In some embodiments, the neuroendocrine cancer is a neuroendocrine lung cancer or a neuroendocrine pancreatic cancer. In some embodiments, the neuroendocrine cancer is a Carcinoid tumor in the lungs, gastrointestinal tract or thymus, Pancreatic neuroendocrine tumor (e.g., Gastrinoma, Insulinoma, Glucagonoma, VIPoma) Medullary thyroid carcinoma, Merkel cell carcinoma, Pheochromocytoma of the adrenal gland, Adrenal cancer, Small cell carcinoma (such as in the lungs), or Large cell carcinoid tumor (such as in the lungs). In some embodiments, the cancer is a SSTR2+ lung neuroendocrine tumor. In some embodiments, the cancer is somatostatin receptor-positive (SSTR+) gastroenteropancreatic neuroendocrine tumor (GEP-NET). In some embodiments, the cancer is small cell lung cancer (SCLC). In some embodiments, the cancer is somatostatin receptor expressing (SSTR+) extensive

stage small cell lung cancer (ES-SCLC). In some embodiments, the SCLC is untreated. In some embodiments, the SCLC is recurrent or refractory. In some embodiments, the subject has received at most 1 cycle of platinum- etoposide and PD-L1 inhibitor therapy. In some embodiments, the cancer is untreated. In some embodiments, the cancer is recurrent or refractory. In some embodiments, the radiopharmaceutical composition is administered to the subject in an amount equivalent to about 1kBq/kg to about 0.2GBq/kg body weight per dose. In some embodiments, the radiopharmaceutical composition is administered to the subject in an amount equivalent to about 5kBq/kg to about 50,000kBq/kg body weight per dose. In some embodiments, the radiopharmaceutical composition is administered to the subject in an amount equivalent to about 20k Bq/kg to about 5,000kBq/kg body weight per dose. In some embodiments, the radiopharmaceutical composition is administered to the subject in an amount equivalent to about 50k Bq/kg to about 500 kBq/kg body weight per dose. In some embodiments, the radiopharmaceutical composition is administered to the subject in an amount equivalent to about 50k Bq/kg to about 200 kBq/kg body weight per dose. In some embodiments, the radiopharmaceutical composition is administered to the subject in an amount equivalent to about 60 kBq/kg to about 150 kBq/kg body weight per dose. In some embodiments, the radiopharmaceutical composition is administered to the subject at a radioactivity of about 1 μ Ci to 1,000 μ Ci. In some embodiments, the radiopharmaceutical composition is administered to the subject at a radioactivity of about 10 μ Ci to 500 μ Ci. In some embodiments, the radiopharmaceutical composition is administered to the subject at a radioactivity of about 100 μ Ci to 500 μ Ci. In some embodiments, the radiopharmaceutical composition is administered to the subject at a radioactivity of about 100 μ Ci to 300 μ Ci. In some embodiments, the radiopharmaceutical composition is administered to the subject at a radioactivity of about 125 μ Ci to 275 μ Ci. In some embodiments, the radiopharmaceutical composition is administered to the subject at a radioactivity of about 125 μ Ci, 175 μ Ci, 225 μ Ci, or 275 μ Ci. In some embodiments, the radiopharmaceutical composition is administered at an 4 to 6-week interval. In some embodiments, the radiopharmaceutical composition is administered at an 4-12-week interval. In some embodiments, the radiopharmaceutical composition is administered at an 8-week interval. In some embodiments, the radiopharmaceutical composition is administered to achieve a cumulative dose in the subject of about 10,000 kBq to about 100,000 kBq. In some embodiments, the radiopharmaceutical composition is administered to achieve a cumulative dose in the subject of about 40,000 kBq to about 70,000 kBq. In some embodiments, the radiopharmaceutical composition comprises ^{225}Ac -DOTA-TOC. In some embodiments, the radiopharmaceutical composition comprises ^{225}Ac -DOTA-TATE. In some embodiments, the radiopharmaceutical

composition comprises ^{225}Ac -DOTA-JR-11. In some embodiments, the radiopharmaceutical composition comprises ^{225}Ac -HA-DOTA-TATE.

[206] In some embodiments, provided herein are methods for killing a cell comprising contacting the cell with a conjugate or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the cell expresses a receptor described herein. In some embodiments, the conjugate or pharmaceutically acceptable salt or solvate thereof binds to a structure on the cell. In some embodiments, the conjugate or pharmaceutically acceptable salt or solvate thereof releases a number of alpha particles by natural radioactive decay. In some embodiments, the conjugate or pharmaceutically acceptable salt or solvate thereof releases a number of beta particles, gamma rays, and/or Auger electrons by natural radioactive decay. The conjugate described herein can kill a cell by radiation. In some embodiments, the conjugate kills the cell directly by radiation. In some embodiments, the radiation creates, in the cell, oxidized bases, abasic sites, single-stranded breaks, double-stranded breaks, DNA crosslink, chromosomal rearrangement, or a combination thereof. The conjugate can kill the cell by inducing double-stranded DNA breaks. The released alpha particles can be sufficient to kill the cell. The released alpha particles can be sufficient to stop cell growth. The conjugate can also kill the cell indirectly via the production of reactive oxygen species (ROS) such as free hydroxyl radicals. In some embodiments, the conjugate kills the cell indirectly by releasing tumor antigens from one or more different cells, which can have vaccine effect. The conjugate can kill the cell by abscopal effect. The cell can be a cancer cell. In some embodiments, the method comprises killing a cell with an alpha-particle emitting radionuclide.

[207] After contacting a cell, the described conjugate can be internalized by the cell. The internalization can be mediated by cell receptors, cell membrane endocytosis, etc. In some embodiments, rapid internalization rate into cancer cells accompanied by a slow externalization rate can offer therapeutic benefit.

[208] In one aspect, the disclosed conjugate or a pharmaceutically acceptable salt or solvate thereof is configured to treat cancer by ablating tumor cells. The conjugate or a pharmaceutically acceptable salt or solvate thereof may not modulate the biology of the tumor cell and/or the surrounding stroma. The conjugate or a pharmaceutically acceptable salt or solvate thereof may not modulate immune cells. The ablating of tumor cells can lead to a downstream immunological cascade.

[209] Non-limiting examples of cancers to be treated by the methods of the present disclosure can include melanoma (e.g., metastatic malignant melanoma), renal cancer (e.g., clear cell carcinoma), prostate cancer (e.g., hormone refractory prostate adenocarcinoma), pancreatic adenocarcinoma, breast cancer, colon cancer, lung cancer (e.g., non-small cell lung cancer, small

cell lung cancer, extensive stage small cell lung cancer), esophageal cancer, squamous cell carcinoma of the head and neck, liver cancer, ovarian cancer, cervical cancer, thyroid cancer, glioblastoma, glioma, leukemia, lymphoma, and other neoplastic malignancies. In some embodiments, a subject or population of subjects to be treated with a radiopharmaceutical composition of the present disclosure have a solid tumor. In some embodiments, a solid tumor is a melanoma, renal cell carcinoma, lung cancer, bladder cancer, breast cancer, cervical cancer, colon cancer, gall bladder cancer, laryngeal cancer, liver cancer, thyroid cancer, stomach cancer, salivary gland cancer, prostate cancer, pancreatic cancer, gastroenteropancreatic neuroendocrine tumor, or Merkel cell carcinoma. In some embodiments, a subject or population of subjects to be treated with a radiopharmaceutical composition of the present disclosure have a hematological cancer. In some embodiments, the subject has a hematological cancer such as Diffuse large B cell lymphoma (“DLBCL”), Hodgkin’s lymphoma (“HL”), Non-Hodgkin’s lymphoma (“NHL”), Follicular lymphoma (“FL”), acute myeloid leukemia (“AML”), or Multiple myeloma (“MM”). In some embodiments, a subject or population of subjects to be treated having the cancer selected from the group consisting of ovarian cancer, lung cancer and melanoma. The cancer can be an SSTR1-associated cancer. The cancer can be an SSTR2-associated cancer. The cancer can be an SSTR3-associated cancer. The cancer can be an SSTR4-associated cancer. The cancer can be an SSTR5-associated cancer. The cancer can be a neuroendocrine cancer, a lymphatic cancer, a pancreatic cancer, a pituitary cancer, a breast cancer, a stomach cancer, medulloblastoma, or neuroblastoma. The cancer can be a neuroendocrine cancer. The neuroendocrine cancer can be recurrent. The neuroendocrine cancer can be refractory to a radiotherapy that comprises beta-particle emitting radionuclide. The neuroendocrine cancer can be a neuroendocrine lung cancer or a neuroendocrine pancreatic cancer. The neuroendocrine cancer can be a Carcinoid tumor in the lungs, gastrointestinal tract or thymus, Pancreatic neuroendocrine tumor (e.g., Gastrinoma, Insulinoma, Glucagonoma, VIPoma) Medullary thyroid carcinoma, Merkel cell carcinoma, Pheochromocytoma of the adrenal gland, Adrenal cancer, Small cell carcinoma (such as in the lungs), or Large cell carcinoid tumor (such as in the lungs). In some embodiments, the neuroendocrine cancer can be a pancreatic neuroendocrine tumor (e.g. gastroenteropancreatic neuroendocrine tumor (GEP-NET)). In some embodiments, the neuroendocrine cancer can be a gastrointestinal neuroendocrine tumor (GI-NET). In some embodiments, the neuroendocrine cancer can be gastroesophageal pancreatic neuroendocrine tumor.

[210] Gastroenteropancreatic neuroendocrine tumors, or GEP-NETs, are rare tumors with an incidence in the U.S. of 5.45 cases per 100,000. Despite this low incidence, many GEP-NETs follow a more indolent disease course than other epithelial malignancies and thus the prevalence

of GEP-NETs in the U.S. is approximately 100,000. GEP-NET tumors can be aggressive and resistant to therapy and based on the Surveillance, Epidemiology, and End Results database, metastatic disease is present at diagnosis in 40-76% of cases. Depending on their morphology and proliferative activity, GEP-NETs can be classified as well-differentiated tumors or poorly differentiated carcinomas. Well-differentiated GEP-NETs can include low-grade (Grade 1, defined as tumors with a mitotic rate of 0 - 1 per 10 high power field, or HPF, or a Ki67 index from 0-2%) and intermediate-grade tumors (Grade 2, defined as tumors with a mitotic rate from 2-20 per 10 HPF or a Ki67 index from 3-20%), whereas poorly differentiated GEP-NETs can be high-grade (Grade 3, with a mitotic rate greater than 20 per 10 HPF or a Ki67 index greater than 20%).

[211] In some embodiments, the site of primary NETs in the digestive tract is the rectum, small intestine, pancreas, stomach, colon, and/or appendix. In some embodiments, the GEP-NET is categorized as hormonally functional (associated with signs and symptoms consistent with excess hormone secretion). In some embodiments, the GEP-NET is categorized as non-functional tumors, with clinical features and aggressiveness depending on the primary tumor site. In some embodiments, the cancer is pancreatic neuroendocrine tumors (pNETs).

[212] In some cases, a subject having GEP-NET has been treated with surgery. In some cases, a subject having GEP-NET is not suitable for surgery treatment. In some cases, a subject having GEP-NET has developed metastatic disease. In some embodiments, the GEP-NET overexpresses somatostatin receptor 2, or SSTR2 on the cell surface. In some embodiments, the subject has been previously treated with Somatostatin analogs, or SSAs. In some embodiments, SSA is administered in combination with a conjugate described herein. In some embodiments, the subject has been previously treated with chemotherapy and molecularly targeted therapies such as everolimus or sunitinib. In some embodiments, chemotherapy and molecularly targeted therapies such as everolimus or sunitinib is administered in combination with a conjugate described herein.

[213] In some embodiments, provided herein are methods and compositions for treating a disease or condition. Exemplary disease or condition includes refractory or recurrent malignancies whose growth may be inhibited using the methods of treatment of the present disclosure. In some embodiments, the disease or condition is a cancer. In some embodiments, the cancer is breast cancer, head and neck squamous cell carcinoma, non-small cell lung cancer, small cell lung cancer, extensive stage small cell lung cancer, hepatocellular cancer, colorectal cancer, gastric adenocarcinoma, pancreatic neuroendocrine tumor (e.g. gastroenteropancreatic neuroendocrine tumor), melanoma, or advanced cancer. In some embodiments, a cancer to be treated by the methods of treatment of the present disclosure is selected from the group consisting of carcinoma, squamous carcinoma, adenocarcinoma, sarcomata, endometrial cancer, breast cancer, ovarian

cancer, cervical cancer, fallopian tube cancer, primary peritoneal cancer, colon cancer, colorectal cancer, squamous cell carcinoma of the anogenital region, melanoma, renal cell carcinoma, lung cancer, non-small cell lung cancer, small cell lung cancer, extensive stage small cell lung cancer, squamous cell carcinoma of the lung, stomach cancer, bladder cancer, gall bladder cancer, liver cancer, thyroid cancer, laryngeal cancer, salivary gland cancer, esophageal cancer, head and neck cancer, glioblastoma, glioma, squamous cell carcinoma of the head and neck, prostate cancer, pancreatic cancer, pancreatic neuroendocrine tumors, gastroenteropancreatic neuroendocrine tumors, mesothelioma, sarcoma, hematological cancer, leukemia, lymphoma, neuroma, and combinations thereof. In some embodiments, a cancer to be treated by the methods of the present disclosure include, for example, carcinoma, squamous carcinoma (for example, cervical canal, eyelid, tunica conjunctiva, vagina, lung, oral cavity, skin, urinary bladder, tongue, larynx, and gullet), and adenocarcinoma (for example, prostate, small intestine, endometrium, cervical canal, large intestine, lung, pancreas, gullet, rectum, uterus, stomach, mammary gland, and ovary). In some embodiments, the cancer is a hypoxic tumor. In some embodiments, the cancer is GEP-NET. In some embodiments, the cancer is small cell lung cancer. In some embodiments, a cancer to be treated by the methods of the present disclosure further include sarcomata (for example, myogenic sarcoma), leukosis, neuroma, melanoma, and lymphoma. In some embodiments, a cancer to be treated by the methods of the present disclosure is lung cancer. In some embodiments, a cancer to be treated by the methods of treatment of the present disclosure is small cell lung cancer (SCLC). In some embodiments, a cancer to be treated by the methods of treatment of the present disclosure is extensive stage small cell lung cancer (ES-SCLC). In some embodiments, the cancer, such as ES-SCLC, has progressed at least 90 days after completion of a first line-therapy. In some embodiments, the cancer has progressed at least 90 days after completion of a first-line therapy comprising a platinum-based therapy. In some embodiments, the cancer has progressed at least 6 months after completion of a first-line therapy. In some embodiments, the cancer has progressed for at least 6 months after completion of a first-line therapy comprising a platinum-based therapy. In some embodiments, the cancer has progressed after at least 1 month, 2 months, 3 months, 6 months, 9 months, 1 year, or 2 years. In some embodiments, the cancer has not progressed. In some embodiments, a cancer to be treated by the methods of the present disclosure is breast cancer. In some embodiments, a cancer to be treated by the methods of treatment of the present disclosure is triple negative breast cancer (TNBC). In some embodiments, a cancer to be treated by the methods of treatment of the present disclosure is pancreatic cancer. In some embodiments, a cancer to be treated by the methods of treatment of the present disclosure is a pancreatic neuroendocrine tumor. In some embodiments, a cancer to be treated by the methods of treatment of the present disclosure is a gastroenteropancreatic neuroendocrine tumor. In some embodiments,

a cancer to be treated by the methods of treatment of the present disclosure is GEP-NET. In some embodiments, a cancer to be treated by the methods of treatment of the present disclosure is gastroesophageal pancreatic neuroendocrine tumor.

[214] In some embodiments, a cancer described herein is untreated. Accordingly, compositions described herein can be used a first line therapy.

[215] In some embodiments, a cancer described herein is recurrent or refractory. For example, the subject having the cancer may have received one or more rounds of standard of care therapy. In some embodiments, the subject has received a radiotherapy that comprises beta-particle emitting radionuclide prior to the administering of the radiopharmaceutical composition (such as ^{177}Lu -DOTA-TATE or ^{177}Lu -DOTA-TOC therapy). In some embodiments, the subject has received platinum-etoposide and PD-L1 inhibitor therapy. In some embodiments, the subject has received ≤ 1 cycle of platinum-etoposide and PD-L1 inhibitor therapy.

[216] In addition to the methods of treatment described above, the radiopharmaceutical compositions described herein can be used to image, and/or as part of a treatment for diseases. Conjugates for imaging applications, e.g., single-photon emission computed tomography (SPECT) and positron emission tomography (PET), can comprise a radionuclide suitable for use as imaging isotopes such as the isotopes in Table 5B. Accordingly, the conjugate can be administered as a companion diagnostic.

[217] In one aspect, provided herein are methods for diagnosing a patient harboring an SSR expressing cancer or tumor comprising administering to the patient a radiopharmaceutical described herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising the same. In one aspect, provided herein are methods for imaging an SSR expressing cancer or tumor comprising administering to the patient a radiopharmaceutical described herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising the same. In some embodiments, the method further comprises selecting or confirming that a tumor in the patient expresses SSR. In some embodiments, the SSR expressing cancer is an SSTR2 expressing cancer. In some embodiments, the method further comprises measuring the concentration of the radiopharmaceutical accumulated in the patient. In some embodiments, the method further comprises measuring the amount of radiation emitted from the radionuclide. In some embodiments, the method further comprises analyzing the elimination or clearance profile of the radiopharmaceutical in the patient. In some embodiments, the method further comprises measuring an elimination half-life of the radiopharmaceutical in the patient. In some embodiments, the method further comprises analyzing the clearance profile of the radiopharmaceutical in the patient. In some embodiments, the method of imaging or diagnosing cancer comprises administering a radiopharmaceutical that comprises a radionuclide of Table 5B,

such as ^{68}Ga . For example, radiopharmaceuticals of the present disclosure can be administered for patient selection purposes, such as to confirm the tumor has the appropriate expression of the SSR target (e.g., SSTR2). As another example, radiopharmaceuticals of the present disclosure can be administered to a patient so that the patient's care team can make sure the radiopharmaceutical is cleared from the body in a suitable timeframe so that undesired irradiation of other tissues is minimized.

[218] In some embodiments, a method described herein comprises administering to a patient two radiopharmaceuticals of the present disclosure. In some embodiments, the two radiopharmaceuticals can have the same targeting ligand. In some embodiments, a method described herein comprises administering (i) a radiopharmaceutical of the present disclosure that comprises a radionuclide of Table 5B, and followed by (i) a radiopharmaceutical of the present disclosure that comprises a radionuclide of Table 5A. In some embodiments, the method comprises administering ^{68}Ga -DOTA-TATE and followed by the administering of ^{225}Ac -DOTA-TATE. In some embodiments, the method comprises administering ^{68}Ga -DOTA-JR-11 and followed by the administering of ^{225}Ac -DOTA-JR-11. In some embodiments, the method comprises administering ^{68}Ga -HA-DOTA-TATE and followed by the administering of ^{225}Ac -HA-DOTA-TATE.

[219] The subject can be 4 to 120 years old. The subject can be 5 to 10, 5 to 15, 5 to 18, 5 to 25, 5 to 35, 5 to 45, 5 to 55, 5 to 65, 5 to 75, 10 to 15, 10 to 18, 10 to 25, 10 to 35, 10 to 45, 10 to 55, 10 to 65, 10 to 75, 15 to 18, 15 to 25, 15 to 35, 15 to 45, 15 to 55, 15 to 65, 15 to 75, 18 to 25, 18 to 35, 18 to 45, 18 to 55, 18 to 65, 18 to 75, 25 to 35, 25 to 45, 25 to 55, 25 to 65, 25 to 75, 35 to 45, 35 to 55, 35 to 65, 35 to 75, 45 to 55, 45 to 65, 45 to 75, 55 to 65, 55 to 75, or 65 to 75 years old. The subject can be at least 5, 10, 15, 18, 25, 35, 45, 55, or 65 years old. The subject can be at most 10, 15, 18, 25, 35, 45, 55, 65, or 75 years old. In some embodiments, the subject has not received a radiotherapy that comprises beta-particle emitting radionuclide prior to the administering of the radiopharmaceutical composition. In some embodiments, the subject has not received a radiotherapy that comprises alpha-particle emitting radionuclide prior to the administering of the radiopharmaceutical composition. In some embodiments, the subject has received a radiotherapy that comprises alpha-particle emitting radionuclide prior to the administering of the radiopharmaceutical composition. In some embodiments, the subject has received a radiotherapy that comprises beta-particle emitting radionuclide prior to the administering of the radiopharmaceutical composition. In some embodiments, the subject has progressive disease following a radiotherapy treatment that comprises beta-particle emitting radionuclide (e.g., a ^{177}Lu labeled somatostatin analog) prior to the administering of the radiopharmaceutical composition. In some embodiments, the subject has previously received

¹⁷⁷Lu-DOTA-TATE treatment. In some embodiments, the subject has previously received ¹⁷⁷Lu-DOTA-TOC treatment. In some embodiments, the subject has not received a therapy comprising a platinum based therapeutic prior to the administering of the radiopharmaceutical composition. In some embodiments, the subject has not received a therapy comprising an immune checkpoint inhibitor prior to the administering of the radiopharmaceutical composition. In some embodiments, the subject has not received a therapy comprising a topoisomerase II inhibitor prior to the administering of the radiopharmaceutical composition. In some embodiments, the subject has received one or fewer cycles of a therapy that comprises a platinum-based compound (e.g. cisplatin), an immune checkpoint inhibitor (e.g. PD-L1 inhibitor), and a topoisomerase II inhibitor (e.g., etoposide) prior to the administering of the radiopharmaceutical composition.

[220] In some embodiments, the subject has been diagnosed with a SSR expressing lesion, neoplasm, cancer, or tumor. In some embodiments, the SSR expressing lesion, neoplasm, cancer, or tumor is characterized quantifying the amount of SSR expression and calculating an H-score. In some embodiments, the H-score is derived by a) staining a tissue biopsy for SSR expression (e.g., SSTR2), b) assigning a cell staining intensity of 0, 1, 2, or 3, c) and multiplying the percentage of cells by their staining intensity level. The H-score has a range of 0 to 300. In some embodiments, the SSR expressing lesion, neoplasm, cancer, or tumor has an H-score of greater than 10. In some embodiments, the SSR expressing lesion, neoplasm, cancer, or tumor has an H-score of greater than 100. In some embodiments, the SSR expressing lesion, neoplasm, cancer, or tumor has an H-score of 11 to 300. In some embodiments, the SSR expressing lesion, neoplasm, cancer, or tumor has an H-score of greater than 200. In some embodiments, the H-score is between 11 and 100. In some embodiments, the H-score is between 50 and 150. In some embodiments, the H-score is between 100 and 200. In some embodiments, the H-score is between 150 and 250. In some embodiments, the H-score is between 200 and 300.

[221] Accordingly, provided herein is a method of treating cancer in a subject in need thereof, the method comprising determining an H-score for a lesion, neoplasm, cancer, or tumor tissue sample of the subject and administering to the subject a radiopharmaceutical composition (such as ²²⁵Ac-DOTA-TATE) described herein. In one aspect, provided herein is a method of treating a subject having an SSTR+ cancer, comprising administering to the subject a radiopharmaceutical composition (such as ²²⁵Ac-DOTA-TATE) described herein. In some embodiments, a cancer sample of the subject has been subjected to a determination of an H-score prior to the administration of a conjugate disclosed herein. In some embodiments, a cancer sample of the subject has been subjected to a determination of an H-score, and wherein the H-score is at least 11. In some embodiments, the method comprises determining an H-score for a tumor cancer of the subject. In some embodiments, the H-score is 0 to 300. In some embodiments, the H-score is

greater than 10. In some embodiments, the H-score is greater than 50. In some embodiments, the H-score is greater than 100. In some embodiments, the H-score is greater than 150. In some embodiments, the H-score is greater than 100. In some embodiments, the H-score is greater than 200. In some embodiments, the H-score is about 120 to 300. In some embodiments, the H-score is about 40 to 300. In some embodiments, the H-score is about 50 to 300. In some embodiments, the H-score is about 100-300. In some embodiments, the H-score is 200-300. An H-score can be calculated according to the method of Example 15.

[222] In one aspect, described herein is a method of treating an SSTR+ cancer in a subject in need thereof, comprising administering to the subject a herein-disclosed radiopharmaceutical composition, wherein an H-score of a cancer sample of the subject is at least 11. In one aspect, described herein is a method of treating a disease in a subject in need thereof, comprising (a) determining a level of SSTR expression in a sample of the subject; and (b) administering to the subject a herein-disclosed radiopharmaceutical composition. In some embodiments, the level of SSTR expression in a sample is determined by calculating an H-Score. In some embodiments, the H-Score is between 11 and 300. In some embodiments, the H-Score is between 11 and 200. In some embodiments, the H-Score is between 11 and 100. In some embodiments, the H-Score is between 101 and 300. In some embodiments, the H-Score is between 101 and 201. In some embodiments, the H-Score is between 201 and 300. In some embodiments, the radiopharmaceutical composition comprises ^{225}Ac -DOTA-TOC. In some embodiments, the radiopharmaceutical composition comprises ^{225}Ac -DOTA-TATE. In some embodiments, the radiopharmaceutical composition comprises ^{225}Ac -HA-DOTA-TATE. In some embodiments, the radiopharmaceutical composition comprises ^{225}Ac -DOTA-JR-11.

[223] In some embodiments, the radiopharmaceutical composition described herein can be administered alone or in combination with one or more additional therapeutic agents. For example, the combination therapy can include a composition comprising a radiopharmaceutical composition described herein co-formulated with, and/or co-administered with, one or more additional therapeutic agents, e.g., one or more anti-cancer agents, e.g., cytotoxic or cytostatic agents, immune checkpoint inhibitors, hormone treatment, vaccines, and/or immunotherapies. In some embodiments, the radiopharmaceutical composition is administered in combination with other therapeutic treatment modalities, including surgery, cryosurgery, and/or chemotherapy. Such combination therapies may advantageously utilize lower dosages of the administered therapeutic agents, thus avoiding possible toxicities or complications associated with the various monotherapies.

[224] When administered in combination, two (or more) different treatments can be delivered to the subject during the course of the subject's affliction with the disorder, e.g., the two or more

treatments are delivered after the subject has been diagnosed with the disorder and before the disorder has been cured or eliminated. In some embodiments, the delivery of one treatment is still occurring when the delivery of the second begins, so that there is overlap. This is sometimes referred to herein as “simultaneous” or “concurrent delivery.” In some embodiments, the delivery of one treatment ends before the delivery of the other treatment begins. In some embodiments of either case, the treatment is more effective because of combined administration. For example, the second treatment is more effective, e.g., an equivalent effect is seen with less of the second treatment, or the second treatment reduces symptoms to a greater extent, than would be seen if the second treatment were administered in the absence of the first treatment, or the analogous situation is seen with the first treatment. In some embodiments, delivery is such that the reduction in a symptom, or other parameter related to the disorder is greater than what would be observed with one treatment delivered in the absence of the other. The effect of the two treatments can be partially additive, wholly additive, or greater than additive. The delivery can be such that an effect of the first treatment delivered is still detectable when the second is delivered.

[225] In some embodiments, the herein-described conjugate is used in combination with a chemotherapeutic agent, e.g., a DNA damaging chemotherapeutic agent. Non-limiting examples of DNA damaging chemotherapeutic agents include topoisomerase I inhibitors, topoisomerase II inhibitors (e.g., etoposide); alkylating agents; DNA intercalators; DNA intercalators and free radical generators such as bleomycin; and nucleoside mimetics. In some embodiments, the herein-described conjugate is used in combination with a platinum-based DNA damaging agent. In some embodiments, the herein-described conjugate is used in combination with carboplatin or cisplatin. In some embodiments, the herein-described conjugate is used in combination with a topoisomerase II inhibitor, for example, etoposide. In some embodiments, the herein-described conjugate is used in combination with a radiation sensitizer, which makes tumor cells more sensitive to radiation therapy. In some embodiments, the herein-described conjugate is used in combination with a DNA damage repair inhibitor (or DNA damage response (DDR) inhibitor). In some embodiments, the herein-described conjugate is used in combination with an immune checkpoint inhibitor. Non-limiting examples of immune checkpoint inhibitors include PD-1 inhibitors (e.g., pembrolizumab sold under the trade name Keytruda, nivolumab sold under the trade name Opdivo, cemiplimab sold under the trade name Libtayo, or dostarlimab sold under the trade name Jemperli), PD-L1 inhibitors (e.g., atezolizumab sold under the trade name Tecentriq, avelumab sold under the trade name Bavencio, or durvalumab sold under the trade name Imfinzi), and CTLA-4 inhibitors (e.g., ipilimumab sold under the trade name Yervoy). In some embodiments, the herein-described conjugate is used in combination with a PD-1 inhibitor. In some embodiments, the herein-described conjugate is used in combination with a PD-L1 inhibitor.

In some embodiments, the herein-described conjugate is used in combination with durvalumab or atezolizumab. In some embodiments, the herein described conjugate is used in combination with durvalumab. In some embodiments, the herein described conjugate is used in combination with atezolizumab. In some embodiments, the herein-described conjugate is used in combination with a CTLA-4 inhibitor.

[226] Durvalumab can be administered in the form of an injectable solution, e.g., in an amount of either 500 mg/10 mL or 120 mg/2.4 mL strength in a single dose vial. In some embodiments, durvalumab is administered as an intravenous infusion. In some embodiments, durvalumab is administered during the induction therapy phase (i.e., 4×12 -day cycles of SoC) for subjects with ES-SCLC and a body weight of ≥ 30 kg at 1500 mg (fixed dose) on the first day of every 3-week (21-day) cycle along with platinum-based chemotherapy and etoposide for a total of 4 cycles. In some embodiments, durvalumab is administered during the maintenance phase, and for subjects with a body weight of ≥ 30 kg, at a dose of 1500 mg (fixed dose) once every 4 weeks until disease progression or unacceptable toxicity. In some embodiments, durvalumab is administered during the maintenance phase, and for subjects with a body weight < 30 kg at a weight-based dosing equivalent to 20 mg/kg in combination with chemotherapy followed by 10 mg/kg every 2 weeks as a single agent. In some embodiments, durvalumab is administered in an amount of 1 mg/kg to 50 mg/kg per dose. In some embodiments, durvalumab is administered in an amount of 5 mg/kg to 15 mg/kg per dose. In some embodiments, durvalumab is administered in an amount of 50 mg to 15000 mg per dose. In some embodiments, durvalumab is administered in an amount of 1000 mg to 2000 mg per dose. In some embodiments, durvalumab is administered in an amount ranging from about 100 mg, 200 mg, 500 mg, 800 mg, or 1000 mg to about 1100 mg, 1200 mg, 1500 mg, 1800 mg, 2000 mg or 3000 mg per dose. In some embodiments, durvalumab is administered in an amount of 1500 mg to 2000 mg per dose. In some embodiments, durvalumab is administered once a week, twice a week, every 2 weeks, every 3 weeks, every 4 weeks, every 5 weeks, every 6 weeks, every 7 weeks, or every 8 weeks. In some embodiments, durvalumab is administered every 3 weeks. In some embodiments, durvalumab is administered every 4 weeks. In some embodiments, durvalumab is administered with a conjugate of the present disclosure with etoposide and cisplatin. In some embodiments, durvalumab is administered with a conjugate of the present disclosure with cisplatin.

[227] Atezolizumab can be administered in the form of an injectable solution of either 840 mg/14 mL or 1200 mg/20 mL strength in a single dose vial. In some embodiments, atezolizumab is administered during the induction therapy phase for subjects with ES-SCLC at 840 mg (fixed dose) on the first day of every 2-week (14-day) cycle along with carboplatin and etoposide for a maximum of 4 cycles. In some embodiments, atezolizumab is administered during the induction

therapy phase for subjects with ES-SCLC at 1200 mg (fixed dose) on the first day of every 3-week (21-day) cycle along with carboplatin and etoposide for a maximum of 4 cycles. In some embodiments, atezolizumab is administered during the induction therapy phase for subjects with ES-SCLC at 1680 mg (fixed dose) on the first day of every 4-week (28-day) cycle along with carboplatin and etoposide for a maximum of 4 cycles. In some embodiments, atezolizumab is administered during the maintenance phase at a dose of 840 mg (fixed dose) once every 2 weeks until disease progression or unacceptable toxicity. In some embodiments, atezolizumab is administered during the maintenance phase at a dose of 1200 mg (fixed dose) once every 3 weeks until disease progression or unacceptable toxicity. In some embodiments, atezolizumab is administered during the maintenance phase at a dose of 1680 mg (fixed dose) once every 4 weeks until disease progression or unacceptable toxicity. In some embodiments, atezolizumab is administered in an amount of 10 mg to 20,000 mg per dose. In some embodiments, atezolizumab is administered in an amount ranging from about 100 mg, 200 mg, 500 mg, 800 mg, or 1000 mg to about 1100 mg, 1200 mg, 1500 mg, 1800 mg, 2000 mg or 3000mg per dose. In some embodiments, atezolizumab is administered in an amount of 1000 mg to 1500 mg per dose. In some embodiments, atezolizumab is administered in an amount of 1100 mg to 1300 mg per dose. In some embodiments, atezolizumab is administered in an amount of 1500 mg to 1700 mg per dose. In some embodiments, atezolizumab is administered in an amount of 1600 mg to 1750 mg per dose. In some embodiments, atezolizumab is administered in an amount of 1500 mg to 2000 mg per dose. In some embodiments, atezolizumab is administered once a week, twice a week, every 2 weeks, every 3 weeks, every 4 weeks, every 5 weeks, every 6 weeks, every 7 weeks, or every 8 weeks. In some embodiments, atezolizumab is administered every 3 weeks. In some embodiments, atezolizumab is administered every 4 weeks. In some embodiments, atezolizumab is administered with a conjugate of the present disclosure with etoposide and carboplatin.

[228] Carboplatin can be administered once every 21 days for a maximum of 4x21-day cycles. In some embodiments, carboplatin is administered by IV infusion over 60 minutes. In some embodiments, carboplatin is administered by IV infusion to achieve an initial target AUC of 5 mg/mL/min as determined by the Calvert Formula (Calvert et al. 1989). The Calvert Formula is $\text{Total Dose (mg)} = (\text{target AUC}) \times (\text{Glomerular Filtration Rate} + 25)$, wherein the glomerular filtration rate (GFR) used in the formula does not exceed 125 mL/min and is considered equivalent to CrCl as determined using the Cockcroft-Gault formula (Cockcroft and Gault, 1976).

[229] Cisplatin can be administered once every 21 days for a maximum of 4x21-day cycles. In some embodiments, cisplatin is administered by IV infusion over 60 minutes. In some embodiments, cisplatin is administered by IV infusion at a dose of 75-80 mg/m² over 60 minutes.

[230] Etoposide can be administered on 3 consecutive days of a 21-day cycle for a maximum of 4x21-day cycles. In some embodiments, etoposide is administered by IV infusion over 60 minutes. In some embodiments, etoposide is administered by IV infusion at a dose of 80-100 mg/mm² for 60 minutes.

[231] In some embodiments, a herein-described conjugate is used in combination with one or more of a chemotherapeutic agents (e.g., a topoisomerase II inhibitor, Everolimus, Sunitinib), a platinum-based agent (e.g., carboplatin or cisplatin), and an immune checkpoint inhibitor (e.g., a PD-L1 inhibitor). In some embodiments, a herein-described conjugate is used in combination with a chemotherapeutic agent (e.g., a topoisomerase II inhibitor), a platinum-based agent (e.g., carboplatin or cisplatin), and an immune checkpoint inhibitor (e.g., a PD-L1 inhibitor). In some embodiments, a herein-described conjugate is used in combination with a cytotoxic chemotherapy. In some embodiments, a herein-described conjugate (such as ²²⁵Ac-DOTA-TATE) is used in combination with Everolimus. In some embodiments, a herein-described conjugate (such as ²²⁵Ac-DOTA-TATE) is used in combination with Sunitinib.

[232] In some embodiments, a herein-described conjugate is used in combination with a Somatostatin analog, such as octreotide and lanreotide.

[233] Co-administration of amino acids with a radiopharmaceutical described herein may reduce kidney uptake of the radiopharmaceutical. In some embodiments, a radiopharmaceutical composition described herein is concurrently administered with an intravenous infusion of one or more amino acids. In some embodiments, a radiopharmaceutical composition described herein is administered after an intravenous infusion of one or more amino acids. In some embodiments, the infusion of the one or more amino acids is administered at least 30 minutes prior to administering a radiopharmaceutical composition described herein. In some embodiments, the infusion of the one or more amino acids is administered at least 6 hours, 3 hours, 1 hour, 30 minutes, 20 minutes, 10 minutes, or 5 minutes prior to administering a radiopharmaceutical composition described herein. In some embodiments, the infusion of the one or more amino acids is administered 10 to 60 minutes prior to administering a radiopharmaceutical composition described herein. In some embodiments, the infusion of the one or more amino acids is completed before initiating a standard of care (SoC) therapy such as platinum (carboplatin or cisplatin) + etoposide +/- PD-L1 inhibitor. In some embodiments, the infusion of the one or more amino acids is completed at least 6 hours, 3 hours, 1 hour, 30 minutes, 20 minutes, 10 minutes, or 5 minutes before initiating a standard of care therapy. In some embodiments, the concentration of the one or more amino acids is about 0.5% to about 10 % w/v. In some embodiments, the one or more amino acids comprise L-arginine and L-lysine. In some embodiments, the one or more amino acids comprise L-arginine hydrochloride and L-lysine hydrochloride. In some embodiments, the concentration of each of the

L-arginine hydrochloride and L-lysine hydrochloride is about 1 to about 100g in about 1 to about 10 L. In some embodiments, the concentration of each of the L-arginine hydrochloride and L-lysine hydrochloride is about 10 to about 50 g in about 1 to about 5 L. In some embodiments, the concentration of each of the L-arginine hydrochloride and L-lysine hydrochloride is about 18 to about 25 g in about 1 to about 2.2 L. In some embodiments, the concentration of each of the L-arginine hydrochloride and L-lysine hydrochloride is 18 to 25 g in 1 to 2.2 L. In some embodiments, the concentration of the one or more amino acids is about 0.1% to about 25 % w/v. In some embodiments, the concentration of the one or more amino acids is about 1% to about 5 % w/v. In some embodiments, the concentration of the one or more amino acids is about 1% to about 3 % w/v. In some embodiments, a radiopharmaceutical described herein is concurrently administered with an infusion of arginine and lysine. In some embodiments, a radiopharmaceutical described herein is concurrently administered with an intravenous infusion of arginine hydrochloride and lysine hydrochloride, where the concentration of arginine hydrochloride and lysine hydrochloride is about 2 % w/v to about 5% w/v. In some embodiments, a radiopharmaceutical described herein is concurrently administered with an intravenous infusion of arginine hydrochloride and lysine hydrochloride, where the concentration of arginine hydrochloride and lysine hydrochloride is about 2.5% w/v. In some embodiments, the intravenous infusion of arginine and lysine is administered before administering a radiopharmaceutical described herein. In some embodiments, the intravenous infusion is administered at least 30 minutes prior to administering a radiopharmaceutical described herein. In some embodiments, the intravenous infusion is administered at least 30 minutes prior to administering a radiopharmaceutical described herein and is continually administered for up to 4 hours total.

[234] The radiopharmaceutical compositions of the current disclosure can be administered by any suitable means, including oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal and epidural and intranasal, and, if desired for local treatment, intralesional administration. The term parenteral as used herein includes e.g., subcutaneous, intravenous, intramuscular, intrasternal, intraperitoneal, and infusion techniques. The term parenteral also includes injections, into the eye or ocular, intravitreal, intrabuccal, transdermal, intranasal, into the brain, including intracranial and intradural, into the joints, including ankles, knees, hips, shoulders, elbows, wrists, and the like, and in suppository form. The radiopharmaceutical compositions can be administered orally. The radiopharmaceutical compositions can be administered by systemic administration. The radiopharmaceutical compositions can be administered parenterally. The radiopharmaceutical compositions can be administered locally at a targeted site.

[235] The radiopharmaceutical compositions described herein can be administered via parenteral injection as liquid solution, which can include other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, preservatives, or excipients. Parenteral injections can be formulated for bolus injection or continuous infusion. The radiopharmaceutical compositions can be formulated in a form suitable for parenteral injection as a sterile suspension, solution or emulsion in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing or dispersing agents. The radiopharmaceutical formulations for parenteral administration can comprise aqueous solutions of the active compounds in water soluble form. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid, gentisic acid, or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates; surfactants such as polysorbate 80; and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. In some embodiments, the radiopharmaceutical composition comprises a reductant. The presence of a reductant can help minimize potential radiolysis. In some embodiments, the reductant is ascorbic acid, gentisic acid, sodium thiosulfate, citric acid, tartaric acid, or a combination thereof.

[236] The radiopharmaceutical compositions can be administered in a manner appropriate to the disease to be treated. An appropriate dose and a suitable duration and frequency of administration can be determined by such factors as the condition of the subject, the type and severity of the subject's disease, the particular form of the active ingredient, and the method of administration. In some embodiments, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (*e.g.*, an improved clinical outcome), or a lessening of symptom severity. Optimal doses are generally determined using experimental models and/or clinical trials. The optimal dose depends upon the body mass, weight, or blood volume of the subject. In some embodiments, the radiopharmaceutical compositions can be administered as part of a first-line therapy. In some embodiments, the radiopharmaceutical compositions can be administered as part of a first-line therapy with existing standard of care, for example, immune checkpoint blockers and DNA damaging agents. In some embodiments, the radiopharmaceutical compositions can be administered as part of a first-line therapy with existing standard of care, for example, immune checkpoint blockers (*e.g.* durvalumab or atezolizumab), platinum agents (*e.g.* cisplatin or carboplatin), and topoisomerase inhibitors (*e.g.* etoposide).

[237] The radiopharmaceutical compositions administered can comprise amounts of conjugates or pharmaceutically acceptable salts or solvates thereof sufficient to deliver a therapeutically effective dose of the particular subject. In some embodiments, the dosage of the conjugate is between about 0.1 pg and about 50 mg per kilogram of body weight, between about 1 µg and about 50 mg per kilogram of body weight, or between about 0.1 and about 10 mg per kilogram of body weight. Therapeutically effective dosages can also be determined at the discretion of a physician. By way of example only, the radiopharmaceutical compositions administered can comprise dose of the conjugate or a pharmaceutically acceptable salt or solvate thereof for methods of treating a disease as described herein is about 0.001 mg/kg to about 1 mg/kg body weight of the subject per dose. In some embodiments, the dose of conjugate or a pharmaceutically acceptable salt or solvate thereof for the described methods is about 0.001 mg to about 1000 mg per dose for the subject being treated. In some embodiments, a conjugate or a pharmaceutically acceptable salt or solvate thereof described herein is administered to a subject at a dosage of from about 0.01 mg to about 500 mg, from about 0.01 mg to about 100 mg, or from about 0.01mg to about 50 mg. In some embodiments, a conjugate or a pharmaceutically acceptable salt or solvate thereof described herein is administered to a subject at a dosage of about 0.01 picomole to about 1 mole, about 0.1 picomole to about 0.1 mole, about 1 nanomole to about 0.1 mole, or about 0.01 micromole to about 0.1 millimole. In some embodiments, a conjugate or a pharmaceutically acceptable salt or solvate thereof described herein is administered to a subject at a dosage of about 0.0001 Gbq to about 1000 Gbq, 0.01 Gbq to about 1000 Gbq, about 0.5 Gbq to about 100 Gbq, or about 1 Gbq to about 50 Gbq. In some embodiments, a conjugate or a pharmaceutically acceptable salt or solvate thereof described herein is administered to a subject at a dosage of about 0.006 Gbq to about 0.011 Gbq. In some embodiments, the radiopharmaceutical composition (or a conjugate or a pharmaceutically acceptable salt or solvate thereof) is administered to a subject in an amount equivalent to about 1kBq/kg to about 100,000kBq/kg, about 5kBq/kg to about 50,000kBq/kg, about 20k Bq/kg to about 5,000kBq/kg, about 50k Bq/kg to about 500 kBq/kg, about 50k Bq/kg to about 200 kBq/kg, or about 70 kBq/kg to about 150 kBq/kg body weight per dose. In some embodiments, the radiopharmaceutical composition (or a conjugate or a pharmaceutically acceptable salt or solvate thereof) is administered in an amount equivalent to about 1kBq/kg to about 100,000kBq/kg body weight per dose. The radiopharmaceutical compositions administered to a subject can comprise a conjugate or a pharmaceutically acceptable salt or solvate thereof in an amount equivalent to about 5kBq/kg to about 50,000kBq/kg body weight per dose. The radiopharmaceutical compositions administered to a subject can comprise a conjugate or a pharmaceutically acceptable salt or solvate thereof in an amount equivalent to about 20kBq/kg to about 5,000kBq/kg body weight per dose. The radiopharmaceutical compositions administered

to a subject can comprise a conjugate or a pharmaceutically acceptable salt or solvate thereof in an amount equivalent to about 50k Bq/kg to about 500 kBq/kg body weight per dose. The radiopharmaceutical compositions administered to a subject can comprise a conjugate or a pharmaceutically acceptable salt or solvate thereof in an amount equivalent to about 70 kBq/kg to about 150 kBq/kg body weight per dose. In some embodiments, the radiopharmaceutical compositions administered to a subject can comprise a conjugate or a pharmaceutically acceptable salt or solvate thereof in an amount equivalent to about 30 kBq/kg to about 150 kBq/kg body weight per dose. In some embodiments, the radiopharmaceutical compositions administered to a subject can comprise a conjugate or a pharmaceutically acceptable salt or solvate thereof in an amount equivalent to about 90 kBq/kg to about 180 kBq/kg body weight per dose. In some embodiments, the radiopharmaceutical compositions administered to a subject can comprise a conjugate or a pharmaceutically acceptable salt or solvate thereof in an amount equivalent to about 30 kBq/kg to about 240 kBq/kg body weight per dose. In some embodiments, the radiopharmaceutical compositions administered to a subject can comprise a conjugate or a pharmaceutically acceptable salt or solvate thereof in an amount equivalent to about 60 kBq/kg to about 120 kBq/kg body weight per dose. In some embodiments, the radiopharmaceutical composition (or a conjugate or a pharmaceutically acceptable salt or solvate thereof) is administered to a subject in an amount equivalent to about 120kBq/kg body weight per dose. In some embodiments, the radiopharmaceutical composition (or a conjugate or a pharmaceutically acceptable salt or solvate thereof) is administered to a subject in an amount equivalent to about 90kBq/kg body weight per dose. In some embodiments, the radiopharmaceutical composition (or a conjugate or a pharmaceutically acceptable salt or solvate thereof) is administered to a subject in an amount equivalent to about 60kBq/kg body weight per dose. The radiopharmaceutical composition can be administered to the subject to achieve a cumulative dose of conjugate or pharmaceutically acceptable salt of solvate thereof in an equivalent of about 1,000 kBq to about 5,000,000 kBq. The radiopharmaceutical composition can be administered to the subject to achieve a cumulative dose of conjugate or pharmaceutically acceptable salt of solvate thereof in an equivalent of about 5,000 kBq to about 1,000,000 kBq. The radiopharmaceutical composition can be administered to the subject to achieve a cumulative dose of conjugate or pharmaceutically acceptable salt of solvate thereof in an equivalent of about 8,000 kBq to about 5,000,000 kBq. The radiopharmaceutical composition can be administered to the subject to achieve a cumulative dose of conjugate or pharmaceutically acceptable salt of solvate thereof in an equivalent of about 10,000 kBq to about 100,000 kBq. The radiopharmaceutical composition can be administered to the subject to achieve a cumulative dose of conjugate or pharmaceutically acceptable salt of solvate thereof in an equivalent of about 20,000 kBq to about 90,000 kBq. The

radiopharmaceutical composition can be administered to the subject to achieve a cumulative dose of conjugate or pharmaceutically acceptable salt or solvate thereof in an equivalent of about 40,000 kBq to about 70,000 kBq. In some embodiments, the radiopharmaceutical composition can be administered to the subject to achieve a cumulative dose of conjugate or pharmaceutically acceptable salt or solvate thereof in an equivalent of about 400 kBq to about 4,000,000 kBq. In some embodiments, the radiopharmaceutical composition can be administered to the subject to achieve a cumulative dose of conjugate or pharmaceutically acceptable salt or solvate thereof in an equivalent of about 20,000 kBq to about 40,000 kBq. In some embodiments, the radiopharmaceutical composition can be administered to the subject to achieve a cumulative dose of conjugate or pharmaceutically acceptable salt or solvate thereof in an equivalent of about 20,000 kBq to about 30,000 kBq. In some embodiments, the radiopharmaceutical composition can be administered to the subject to achieve a cumulative dose of conjugate or pharmaceutically acceptable salt or solvate thereof in an equivalent of about 30,000 kBq to about 40,000 kBq. In some embodiments, the radiopharmaceutical composition can be administered to the subject to achieve a cumulative dose of conjugate or pharmaceutically acceptable salt or solvate thereof in an equivalent of about 40,000 kBq to about 50,000 kBq. In some embodiments, the radiopharmaceutical composition can be administered to the subject to achieve a cumulative dose of conjugate or pharmaceutically acceptable salt or solvate thereof in an equivalent of about 40,000 kBq to about 100,000 kBq. In some embodiments, the radiopharmaceutical composition can be administered to the subject to achieve a maximum cumulative dose of conjugate or pharmaceutically acceptable salt or solvate thereof in an equivalent of about 60,000 kBq. In some embodiments, the radiopharmaceutical composition can be administered to the subject to achieve a maximum cumulative dose of conjugate or pharmaceutically acceptable salt or solvate thereof in an equivalent of about 40,800 kBq. In some embodiments, the radiopharmaceutical composition is administered to deliver a radioactivity dose of about 1 μ Ci to 1,000 μ Ci. In some embodiments, the radiopharmaceutical composition is administered to deliver a radioactivity dose of about 10 to 500 μ Ci. In some embodiments, the radiopharmaceutical composition is administered to deliver a radioactivity dose of about 100 to 500 μ Ci. In some embodiments, the radiopharmaceutical composition is administered to deliver a radioactivity dose of about 100 to 300 μ Ci. In some embodiments, the radiopharmaceutical composition is administered to deliver a radioactivity dose of about 100 to 300 μ Ci. In some embodiments, the radiopharmaceutical composition is administered to deliver a radioactivity dose of about 125 to 275 μ Ci. In some embodiments, the radiopharmaceutical composition is administered to deliver a radioactivity dose of about 125 μ Ci, 175 μ Ci, 225 μ Ci, or 275 μ Ci. In some embodiments, the radiopharmaceutical composition is administered to deliver a radioactivity dose of about 125 μ Ci. In some embodiments, the

radiopharmaceutical composition is administered to deliver a radioactivity dose of about 175 μCi . In some embodiments, the radiopharmaceutical composition is administered to deliver a radioactivity dose of about 225 μCi . In some embodiments, the radiopharmaceutical composition is administered to deliver a radioactivity dose of about 275 μCi . In some embodiments, the dose is administered once a day, 1 to 3 times a week, 1 to 4 times a month, or 1 to 12 times a year. The radiopharmaceutical compositions can be administered at a 2-week interval. The radiopharmaceutical compositions can be administered at a 4-week interval. The radiopharmaceutical compositions can be administered at a 6-week interval. The radiopharmaceutical compositions can be administered at an 8-week interval. The radiopharmaceutical compositions can be administered at a 10-week interval. The radiopharmaceutical compositions can be administered at a 12-week interval. The radiopharmaceutical compositions can be administered at a 15-week interval. The radiopharmaceutical composition can be administered at a 20-week interval. The radiopharmaceutical composition can be administered in cycles. For example, the radiopharmaceutical composition can be administered in 1-20 cycles. In some embodiments, the radiopharmaceutical composition is administered for 1-10 cycles. In some embodiments, the radiopharmaceutical composition is administered for 1-5 cycles. In some embodiments, the radiopharmaceutical composition is administered for 3-9 cycles. In some embodiments, the radiopharmaceutical composition is administered for 1 cycle. In some embodiments, the radiopharmaceutical composition is administered for 2 cycles. In some embodiments, the radiopharmaceutical composition is administered for 3 cycles. In some embodiments, the radiopharmaceutical composition is administered for 4 cycles. In some embodiments, the radiopharmaceutical composition is administered for 5 cycles. In some embodiments, the radiopharmaceutical composition is administered for 6 cycles. In some embodiments, the radiopharmaceutical composition is administered for 7 cycles. In some embodiments, the radiopharmaceutical composition is administered for 8 cycles. In some embodiments, the radiopharmaceutical composition is administered for 9 cycles. In some embodiments, the radiopharmaceutical composition is administered for 10 cycles. In some embodiments, the radiopharmaceutical composition is administered for 11 cycles. In some embodiments, the radiopharmaceutical composition is administered for 12 cycles. In some embodiments, each cycle includes one administration every 8 weeks. In some embodiments, each cycle includes one administration every 4-6 weeks. In some embodiments, each cycle includes one administration every 1-12 weeks. In some embodiments, each cycle includes one administration every 2-8 weeks. In some embodiments, each cycle includes one administration every 4 weeks. In some embodiments, each cycle includes one administration every 5 weeks. In some embodiments, each

cycle includes one administration every 6 weeks. In some embodiments, each cycle includes one administration every 12 weeks. In some embodiments, the radiopharmaceutical composition comprises ^{225}Ac -DOTA-TATE. In some embodiments, the radiopharmaceutical composition comprises ^{225}Ac -DOTA-TOC. In some embodiments, the radiopharmaceutical composition comprises ^{225}Ac -DOTA-JR-11. In some embodiments, the radiopharmaceutical composition comprises ^{225}Ac -HA-DOTA-TATE.

[238] The pharmaceutical compositions can be packaged in unit dosage form for ease of administration and uniformity of dosage. A unit dosage form can refer to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the pharmaceutical carrier or excipient. In some embodiments, the unit dosage has a volume of 100 to 250 mL. In some embodiments, the unit dosage has a volume of 25 to 100 mL. In some embodiments, the unit dosage has a volume of 5 to 25 mL. In some embodiments, the unit dosage has a volume of 1 to 1000 mL. In some embodiments, the unit dosage has a volume of 1 to 10 mL. In some embodiments, the unit dosage has a volume of 8 to 15 mL. In some embodiments, the unit dosage has a volume of 10 to 15 mL. In some embodiments, the unit dosage has a volume of 8 mL. In some embodiments, the unit dosage has a volume of 9 mL. In some embodiments, the unit dosage has a volume of 10 mL. In some embodiments, the unit dosage has a volume of 11 mL. In some embodiments, the unit dosage has a volume of 12 mL. In some embodiments, the unit dosage has a volume of 13 mL. In some embodiments, the unit dosage has a volume of 14 mL. In some embodiments, the unit dosage has a volume of 15 mL. In some embodiments, the unit dosage has a volume of 16 mL. In some embodiments, the unit dosage has a volume of 17 mL. In some embodiments, the unit dosage has a volume of 18 mL. In some embodiments, the unit dosage has a volume of 19 mL. In some embodiments, the unit dosage has a volume of 20 mL. In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-TATE in an amount equivalent to 146 – 275 μCi . In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-TATE in an amount equivalent to 100–300 μCi . In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-TOC. In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-JR-11. In some embodiments, the radiopharmaceutical composition comprises ^{225}Ac -HA-DOTA-TATE.

[239] In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-TATE in an amount equivalent to 10 – 500 μCi . In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-TATE in an amount equivalent to 500 – 2000 μCi . In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-TATE in an amount equivalent to more than 500 μCi . In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-TATE in an amount equivalent to 10 – 100 μCi . In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-TATE in an amount equivalent to 10 – 50

μCi. In some embodiments, the unit dosage comprises ²²⁵Ac-DOTA-TATE in an amount equivalent to 100 – 200 μCi. In some embodiments, the unit dosage comprises ²²⁵Ac-DOTA-TATE in an amount equivalent to 120 – 300 μCi. In some embodiments, the unit dosage comprises ²²⁵Ac-DOTA-TATE in an amount equivalent to 200 – 400 μCi. In some embodiments, the unit dosage comprises ²²⁵Ac-DOTA-TATE in an amount equivalent to 200 – 500 μCi. In some embodiments, the unit dosage comprises ²²⁵Ac-DOTA-TATE in an amount equivalent to 150 – 300 μCi. In some embodiments, the unit dosage comprises ²²⁵Ac-DOTA-TATE in an amount equivalent to 146 – 275 μCi. In some embodiments, the unit dosage comprises ²²⁵Ac-DOTA-TATE in an amount equivalent to 146 – 275 μCi in a 12 mL solution.

[240] In some embodiments, the unit dosage comprises ²²⁵Ac-DOTA-TATE in an amount equivalent to 45-114 μg of DOTATATE. In some embodiments, the unit dosage comprises ²²⁵Ac-DOTA-TATE in an amount equivalent to 5 to 1000 μg of DOTATATE. In some embodiments, the unit dosage comprises ²²⁵Ac-DOTA-TATE in an amount equivalent to 0.5 to 10,000 μg of DOTATATE. In some embodiments, the unit dosage comprises ²²⁵Ac-DOTA-TATE in an amount equivalent to 20 to 200 μg of DOTATATE. In some embodiments, the unit dosage comprises ²²⁵Ac-DOTA-TATE in an amount equivalent to 10 to 50 μg of DOTATATE. In some embodiments, the unit dosage comprises ²²⁵Ac-DOTA-TATE in an amount equivalent to 50 to 150 μg of DOTATATE. In some embodiments, the unit dosage comprises ²²⁵Ac-DOTA-TATE in an amount equivalent to 1 to 100 μg of DOTATATE. In some embodiments, the unit dosage comprises ²²⁵Ac-DOTA-TATE in an amount equivalent to 1 to 200 μg of DOTATATE. In some embodiments, the unit dosage comprises ²²⁵Ac-DOTA-TATE in an amount equivalent to 100 to 500 μg of DOTATATE. In some embodiments, the unit dosage comprises ²²⁵Ac-DOTA-TATE in an amount equivalent to 25 to 150 μg of DOTATATE. In some embodiments, the unit dosage comprises ²²⁵Ac-DOTA-TATE in an amount equivalent to about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, or 160 μg of DOTATATE.

[241] In some embodiments, the unit dosage comprises a radiopharmaceutical conjugate in an amount equivalent to 10 – 500 μCi. In some embodiments, the unit dosage comprises a radiopharmaceutical conjugate in an amount equivalent to 500 – 2000 μCi. In some embodiments, the unit dosage comprises a radiopharmaceutical conjugate in an amount equivalent to more than 500 μCi. In some embodiments, the unit dosage comprises a radiopharmaceutical conjugate in an amount equivalent to 10 – 100 μCi. In some embodiments, the unit dosage comprises a radiopharmaceutical conjugate in an amount equivalent to 10 – 50 μCi. In some embodiments, the unit dosage comprises a radiopharmaceutical conjugate in an amount equivalent to 100 – 200 μCi. In some embodiments, the unit dosage comprises a radiopharmaceutical conjugate in an

amount equivalent to 120 – 300 μCi . In some embodiments, the unit dosage comprises a radiopharmaceutical conjugate in an amount equivalent to 200 – 400 μCi . In some embodiments, the unit dosage comprises a radiopharmaceutical conjugate in an amount equivalent to 200 – 500 μCi . In some embodiments, the unit dosage comprises a radiopharmaceutical conjugate in an amount equivalent to 150 – 300 μCi . In some embodiments, the unit dosage comprises a radiopharmaceutical conjugate in an amount equivalent to 146 – 275 μCi . In some embodiments, the unit dosage comprises a radiopharmaceutical conjugate in an amount equivalent to 146 – 275 μCi in a 12 mL solution. In some embodiments, the radiopharmaceutical conjugate is ^{225}Ac -DOTA-TOC. In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-JR-11. In some embodiments, the radiopharmaceutical composition comprises ^{225}Ac -HA-DOTA-TATE. In some embodiments, the radiopharmaceutical composition comprises ^{225}Ac -DOTA-TATE.

[242] In some embodiments, the unit dosage comprises a radiopharmaceutical conjugate in an amount equivalent to 45-114 μg of DOTATOC. In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-TOC in an amount equivalent to 5 to 1000 μg of DOTATOC. In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-TOC in an amount equivalent to 0.5 to 10,000 μg of DOTATOC. In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-TOC in an amount equivalent to 20 to 200 μg of DOTATOC. In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-TOC in an amount equivalent to 10 to 50 μg of DOTATOC. In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-TOC in an amount equivalent to 50 to 150 μg of DOTATOC. In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-TOC in an amount equivalent to 1 to 100 μg of DOTATOC. In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-TOC in an amount equivalent to 1 to 200 μg of DOTATOC. In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-TOC in an amount equivalent to 100 to 500 μg of DOTATOC. In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-TOC in an amount equivalent to 25 to 150 μg of DOTATOC. In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-TOC in an amount equivalent to about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, or 160 μg of DOTATOC.

[243] In some embodiments, the unit dosage comprises a radiopharmaceutical conjugate in an amount equivalent to 45-114 μg of HA-DOTA-TATE. In some embodiments, the unit dosage comprises ^{225}Ac -HA-DOTA-TATE in an amount equivalent to 5 to 1000 μg of HA-DOTA-TATE. In some embodiments, the unit dosage comprises ^{225}Ac -HA-DOTA-TATE in an amount equivalent to 0.5 to 10,000 μg of HA-DOTA-TATE. In some embodiments, the unit dosage comprises ^{225}Ac -HA-DOTA-TATE in an amount equivalent to 20 to 200 μg of HA-DOTA-TATE. In some embodiments, the unit dosage comprises ^{225}Ac -HA-DOTA-TATE in an amount equivalent to 10 to 50 μg of HA-DOTA-TATE. In some embodiments, the unit dosage comprises

^{225}Ac -HA-DOTA-TATE in an amount equivalent to 50 to 150 μg of HA-DOTA-TATE. In some embodiments, the unit dosage comprises ^{225}Ac -HA-DOTA-TATE in an amount equivalent to 1 to 100 μg of HA-DOTA-TATE. In some embodiments, the unit dosage comprises ^{225}Ac -HA-DOTA-TATE in an amount equivalent to 1 to 200 μg of HA-DOTA-TATE. In some embodiments, the unit dosage comprises ^{225}Ac -HA-DOTA-TATE in an amount equivalent to 100 to 500 μg of HA-DOTA-TATE. In some embodiments, the unit dosage comprises ^{225}Ac -HA-DOTA-TATE in an amount equivalent to 25 to 150 μg of HA-DOTA-TATE. In some embodiments, the unit dosage comprises ^{225}Ac -HA-DOTA-TATE in an amount equivalent to about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, or 160 μg of HA-DOTA-TATE.

[244] In some embodiments, the unit dosage comprises a radiopharmaceutical conjugate in an amount equivalent to 45-114 μg of DOTA-JR-11. In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-JR-11 in an amount equivalent to 5 to 1000 μg of DOTA-JR-11. In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-JR-11 in an amount equivalent to 0.5 to 10,000 μg of DOTA-JR-11. In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-JR-11 in an amount equivalent to 20 to 200 μg of DOTA-JR-11. In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-JR-11 in an amount equivalent to 10 to 50 μg of DOTA-JR-11. In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-JR-11 in an amount equivalent to 50 to 150 μg of DOTA-JR-11. In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-JR-11 in an amount equivalent to 1 to 100 μg of DOTA-JR-11. In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-JR-11 in an amount equivalent to 1 to 200 μg of DOTA-JR-11. In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-JR-11 in an amount equivalent to 100 to 500 μg of DOTA-JR-11. In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-JR-11 in an amount equivalent to 25 to 150 μg of DOTA-JR-11. In some embodiments, the unit dosage comprises ^{225}Ac -DOTA-JR-11 in an amount equivalent to about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, or 160 μg of DOTA-JR-11.

[245] In some embodiments, radiopharmaceutical compositions described herein are formulated in a unit dosage form stored in a glass vial.

[246] In some embodiments, the radiopharmaceutical compositions described herein can comprise compounds exist as solvates. This disclosure provides for methods of treating diseases by administering such solvates. This disclosure further provides for methods of treating diseases by administering such solvates as radiopharmaceutical compositions.

[247] Disclosure of the present application is further illustrated in the following list of embodiments, which are given for illustration purposes only and are not intended to limit the disclosure in any way.

[248] **Embodiment 1:** A liquid radiopharmaceutical composition comprising or consisting of:

- (a) ^{225}Ac -DOTA-TATE, wherein the ^{225}Ac -DOTA-TATE is present in the radiopharmaceutical composition at a concentration equivalent to about 10 mCi/L to about 30 mCi/L;
 - (b) sodium L-ascorbate, wherein the sodium L-ascorbate is present in the radiopharmaceutical composition at a concentration of about 90 mM to about 110 mM;
 - (c) diethylenetriamine pentaacetate (DTPA), wherein the DTPA is present in the radiopharmaceutical composition at a concentration of about 0.04 mg/mL to about 0.06 mg/mL; and
 - (d) an aqueous vehicle, wherein the aqueous vehicle is sodium chloride saline solution at a concentration of about 0.9% w/w;
- wherein the radiopharmaceutical composition is a solution, and
wherein the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content as ^{225}Ac -DOTA-TATE after 120 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC).

[249] **Embodiment 2:** The liquid radiopharmaceutical composition of embodiment 1, wherein the radiopharmaceutical composition retains at least 95 % of the ^{225}Ac content as ^{225}Ac -DOTA-TATE after 120 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC).

[250] **Embodiment 3:** A liquid radiopharmaceutical composition comprising or consisting of:

- (a) ^{225}Ac -DOTA-TATE, wherein the ^{225}Ac -DOTA-TATE is present in the radiopharmaceutical composition at a concentration equivalent to about 10 mCi/L to about 30 mCi/L;
- (b) sodium L-ascorbate, wherein the sodium L-ascorbate is present in the radiopharmaceutical composition at a concentration of about 90 mM to about 110 mM;
- (c) diethylenetriamine pentaacetate (DTPA), wherein the DTPA is present in the radiopharmaceutical composition at a concentration of about 0.04 mg/mL to about 0.06 mg/mL; and
- (d) an aqueous vehicle, wherein the aqueous vehicle is sodium chloride saline solution at a concentration of about 0.9% w/w;

wherein the radiopharmaceutical composition is a solution, and
wherein the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content bound as part of the conjugate after 120 hours at about 20°C to about 25°C as determined by high performance liquid chromatography/fraction collection (HPLC-FC).

[251] Embodiment 4: The radiopharmaceutical composition of embodiment 3, wherein the radiopharmaceutical composition retains at least 95 % of the ^{225}Ac content bound as part of the conjugate after 120 hours at about 20°C to about 25°C as determined by high performance liquid chromatography/fraction collection (HPLC-FC).

[252] Embodiment 5: The liquid radiopharmaceutical composition of any one of embodiments 1-4, wherein the ^{225}Ac -DOTA-TATE is present in the radiopharmaceutical composition at a concentration equivalent to about 10 mCi/L to about 25 mCi/L.

[253] Embodiment 6: The liquid radiopharmaceutical composition of any one of embodiments 1-5, wherein the ^{225}Ac -DOTA-TATE is present in the radiopharmaceutical composition at a concentration equivalent to about 12 mCi/L to 23 mCi/L.

[254] Embodiment 7: The liquid radiopharmaceutical composition of any one of embodiments 1-6, wherein the ^{225}Ac -DOTA-TATE is present in the radiopharmaceutical composition at a concentration equivalent to about 40 µg to about 120 µg of the DOTA-TATE.

[255] Embodiment 8: The liquid radiopharmaceutical composition of any one of embodiments 1 to 47 wherein the sodium L-ascorbate is present in the radiopharmaceutical composition at a concentration of about 100mM.

[256] Embodiment 9: The liquid radiopharmaceutical composition of any one of embodiments 1 to 8, wherein the DTPA is present in the radiopharmaceutical composition at a concentration of about 0.05mg/mL.

[257] Embodiment 10: The liquid radiopharmaceutical composition of any one of embodiments 1 to 9, wherein the composition retains at least 90 % of the ^{225}Ac content as ^{225}Ac -DOTA-TATE after 168 hours at about 20°C to about 25°C.

[258] Embodiment 11: The liquid radiopharmaceutical composition of any one of embodiments 1 to 10, wherein the composition retains at least 90 % of the ^{225}Ac content as ^{225}Ac -DOTA-TATE after 192 hours at about 20°C to about 25°C.

[259] Embodiment 12: The liquid radiopharmaceutical composition of any one of embodiments 1 to 11, wherein the radiopharmaceutical composition is formulated as a unit dose form that contains about 12mL of the solution.

[260] Embodiment 13: The liquid radiopharmaceutical composition of embodiment 1 or 3, comprising or consisting of:

- (a) ^{225}Ac -DOTA-TATE present in the radiopharmaceutical composition at a concentration equivalent to 10 mCi/L to 25 mCi/L;
- (b) sodium L-ascorbate present in the radiopharmaceutical composition at a concentration of about 100 mM;
- (c) DTPA present in the radiopharmaceutical composition at a concentration of about 0.05 mg/mL; and
- (d) sodium chloride saline solution at a concentration of about 0.9% w/w.

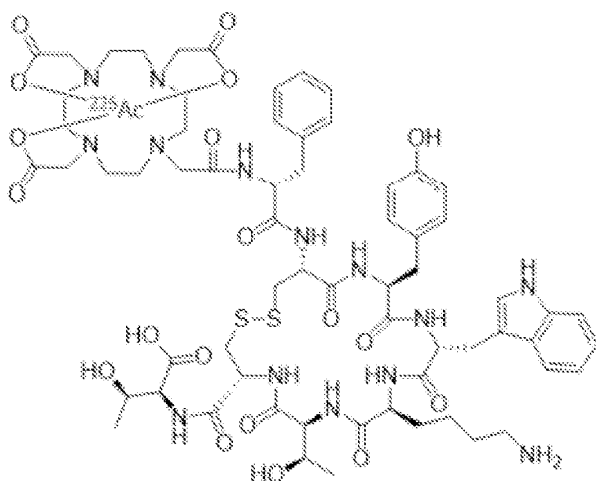
[261] Embodiment 14: The liquid radiopharmaceutical composition of embodiment 1 or 3, wherein the liquid radiopharmaceutical composition is formulated as a unit dose form that has about 12mL of the solution, and wherein the liquid radiopharmaceutical composition comprising or consists of:

- (a) ^{225}Ac -DOTA-TATE present in the radiopharmaceutical composition in an amount of 146 – 275 μCi in the about 12 mL solution;
- (b) sodium L-ascorbate present in the radiopharmaceutical composition at a concentration of about 18.5 mg/mL;
- (c) DTPA present in the radiopharmaceutical composition at a concentration of about 0.05 mg/mL; and
- (d) sodium chloride saline solution at a concentration of about 0.9% w/w.

[262] Embodiment 15: The liquid radiopharmaceutical composition of any one of embodiments 1 to 14, wherein a pH of the liquid radiopharmaceutical composition is about 5.5 to about 7.0.

[263] Embodiment 16: The liquid radiopharmaceutical composition of any one of embodiments 1 to 15, wherein the radiopharmaceutical composition is formulated for IV infusion.

[264] Embodiment 17: The liquid radiopharmaceutical composition of any one of embodiments 1 to 16, wherein the ^{225}Ac -DOTA-TATE has a structure illustrated as



[265] Embodiment 18: A method of treating a somatostatin receptor-positive (SSTR+) neuroendocrine tumor in a subject in need thereof, comprising administering to the subject an effective amount of a liquid radiopharmaceutical composition, wherein the liquid radiopharmaceutical composition comprising or consists of:

- (a) ^{225}Ac -DOTA-TATE, wherein the ^{225}Ac -DOTA-TATE is present in the radiopharmaceutical composition at a concentration equivalent to about 10 mCi/L to about 30 mCi/L;
 - (b) sodium L-ascorbate, wherein the sodium L-ascorbate is present in the radiopharmaceutical composition at a concentration of about 90 mM to about 110 mM;
 - (c) diethylenetriamine pentaacetate (DTPA), wherein the DTPA is present in the radiopharmaceutical composition at a concentration of about 0.04 mg/mL to about 0.06 mg/mL; and
 - (d) an aqueous vehicle, wherein the aqueous vehicle is sodium chloride saline solution at a concentration of about 0.9% w/w;
- wherein the radiopharmaceutical composition is a solution, and wherein the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content as ^{225}Ac -DOTA-TATE after 120 hours at about 20° to about 25°C as determined by radio thin-layer chromatography (radio-TLC).

[266] Embodiment 19: The method of embodiment 18, wherein the radiopharmaceutical composition retains at least 95 % of the ^{225}Ac content as ^{225}Ac -DOTA-TATE after 120 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC).

[267] Embodiment 20: A method of treating a somatostatin receptor-positive (SSTR+) neuroendocrine tumor in a subject in need thereof, comprising administering to the subject an

effective amount of a liquid radiopharmaceutical composition, wherein the liquid radiopharmaceutical composition comprising or consists of:

- (a) ^{225}Ac -DOTA-TATE, wherein the ^{225}Ac -DOTA-TATE is present in the radiopharmaceutical composition at a concentration equivalent to about 10 mCi/L to about 30 mCi/L;
- (b) sodium L-ascorbate, wherein the sodium L-ascorbate is present in the radiopharmaceutical composition at a concentration of about 90 mM to about 110 mM;
- (c) diethylenetriamine pentaacetate (DTPA), wherein the DTPA is present in the radiopharmaceutical composition at a concentration of about 0.04 mg/mL to about 0.06 mg/mL; and
- (d) an aqueous vehicle, wherein the aqueous vehicle is sodium chloride saline solution at a concentration of about 0.9% w/w;

wherein the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content bound as part of the conjugate after 120 hours at about 20°C to about 25°C as determined by high performance liquid chromatography/fraction collection (HPLC-FC).

[268] Embodiment 21: The method of embodiment 20, wherein the radiopharmaceutical composition retains at least 95 % of the ^{225}Ac content bound as part of the conjugate after 120 hours at about 20°C to about 25°C as determined by high performance liquid chromatography/fraction collection (HPLC-FC).

[269] Embodiment 22: The method of any one of embodiments 18-21, wherein the neuroendocrine tumor is gastroenteropancreatic neuroendocrine tumor (GEP-NET).

[270] Embodiment 23: The method of any one of embodiments 18-22, wherein, prior to the administering of the liquid radiopharmaceutical composition, the subject received ^{177}Lu -DOTA-TATE or ^{177}Lu -DOTA-TOC treatment and the tumor has progressed.

[271] Embodiment 24: The method of any one of embodiments 18-23, wherein the radiopharmaceutical composition is administered to the subject in an amount equivalent to about 60 kBq/kg body weight to 120 kBq/kg body weight per dose.

[272] Embodiment 25: The method of any one of embodiments 18-24, wherein the radiopharmaceutical composition is administered at an 8-week interval.

[273] Embodiment 26: The method of any one of embodiments 18-25, wherein the ^{225}Ac -DOTA-TATE is present in the radiopharmaceutical composition at a concentration equivalent to about 10 mCi/L to about 25 mCi/L.

[274] Embodiment 27: The method of embodiment 18 or 20, wherein the liquid radiopharmaceutical composition comprises or consists of:

- (a) ^{225}Ac -DOTA-TATE present in the radiopharmaceutical composition at a concentration equivalent to 10 mCi/L to 25 mCi/L;
- (b) sodium L-ascorbate present in the radiopharmaceutical composition at a concentration of about 100 mM;
- (c) DTPA present in the radiopharmaceutical composition at a concentration of about 0.05 mg/mL; and
- (d) sodium chloride saline solution at a concentration of about 0.9% w/w.

[275] Embodiment 28: The method of embodiment 18 or 20, wherein the liquid radiopharmaceutical composition is formulated as a unit dose form that has about 12mL of the solution, and wherein the liquid radiopharmaceutical composition comprises or consists of:

- (a) ^{225}Ac -DOTA-TATE present in the radiopharmaceutical composition in an amount of 146 – 275 μCi in about 12 mL solution;
- (b) sodium L-ascorbate present in the radiopharmaceutical composition at a concentration of about 18.5 mg/mL;
- (c) DTPA present in the radiopharmaceutical composition at a concentration of about 0.05 mg/mL; and
- (d) sodium chloride saline solution at a concentration of about 0.9% w/w.

[276] Although the present disclosure and its advantages have been described in detail, it should be understood that various changes, substitutions and alterations can be made herein without departing from the spirit and scope of the disclosure as defined in the appended claims.

[277] The present disclosure is further illustrated in the following Examples which are given for illustration purposes only and are not intended to limit the disclosure in any way.

EXAMPLES

Example 1. Conjugate synthesis

[278] A typical procedure to synthesize of ^{225}Ac -DOTA-TATE was achieved by reacting DOTA-TATE acetate (28 μg , 28 μL) from 1.0 mg/mL water solution) with ^{225}Ac - AcCl_3 (6.8 MBq or 0.2 mCi, 22 μL) from 10 $\mu\text{Ci}/\mu\text{L}$ HCl (0.04M, aqueous) solution. The DOTA-TATE acetate was diluted to 150 μL with sodium acetate/acetic acid buffer solution (0.4 M, pH = 6.50). ^{225}Ac - AcCl_3 HCl solution was added. The reaction mixture of total volume of 200 μL was mixed with vortex mixture, then heated at 90°C for 15 min at a shaking speed of 500 rpm. Upon completion, the mixture was directly diluted into the desired formulation described below.

[279] Radio-TLC was performed at time 0 hour to determine radiochemical yield of the labeling reaction with the following protocol: 1 μL of the reaction mixture was spotted onto a TLC plate (Agilent A120B12, plate size 11.4 x 2.0 cm) at 1.5 cm from the bottom edge. The TLC was developed with 10 mM DTPA water solution (pH=7.0, adjusted by 1.0 M NaOH) until the eluent

reaches 1.5 cm from the top edge (or in 15 mins). After drying in an incubator at a temperature of 38°C, the radio-TLC conversion was analyzed at different time points with a radio-TLC reader (Eckert & Ziegler AR-2000) set at High Voltage=1000 (to ensure alpha detection) until the ratio between labeled product and the free Ac225 ion no longer change (typically after 6-8 hours of TLC separation to ensure equilibrium between Ac225 and daughter nuclides). The typical radiochemical yield of [²²⁵Ac]Ac-DOTA-TATE syntheses were found > 99.0 (±0.5) %, Molar activity is 10 mCi/μmol.

Example 2. Broad scope screening of excipients

[280] Upon completion of the radiolabeling, the reaction mixture described in example 1 was immediately diluted in the stabilizing formulation in 30 x fold (v/v), or to 0.03 mCi/ml. The formulations were buffered with sodium acetate-acetic acid 0.4 M solution to pH 5.80 (±0.10). A signal component excipient as stabilizing agent at 1 mg/ml in the buffer, except EtOH where 10 % (v/v) was presented. Sodium L-Ascorbate/L-Ascorbic acid buffer was adjusted to pH 5.80 (±0.10). Water for Injection (WFI) with the same dilution without any excipient is used as the control formulation. The mixture was kept at room temperature (25°C). Purity of [²²⁵Ac]Ac-DOTA-TATE was checked at different time points by radio-TLC as described in the Table 6 below. Purity is described as the ²²⁵Ac present in [²²⁵Ac]Ac-DOTA-TATE divided by total ²²⁵Ac content at that time point.

Table 6

Excipients	Percentage of ²²⁵ Ac present in [²²⁵ Ac]Ac-DOTA-TATE		
	0 hour after mixing	24 hours after mixing	48 hours after mixing
Water for injection (WFI)	99.42	92.43	88.85
Sodium Ascorbate, pH 5.8	99.42	95.42	92.21
Dextran (60-90), Clinical grade	99.42	94.91	86.80
DTPA	99.42	95.77	91.38
L-Methionine	99.42	93.39	89.58
Thiourea	99.42	94.87	89.97
L-Lysine	99.42	95.45	89.52
Catechin hydrate	99.42	95.41	95.64
N-Acetyl-L-Cysteine	99.42	91.19	87.41
L-Glutathione	99.42	91.18	85.56
10% EtOH	99.42	96.35	92.16
Citric Acid	99.42	90.20	82.18
Salicylic Acid	99.42	93.08	87.65

Excipients	Percentage of ^{225}Ac present in [^{225}Ac]Ac-DOTA-TATE		
	0 hour after mixing	24 hours after mixing	48 hours after mixing
Sodium Bisulfite	98.61	0	N/A
Lipoic Acid	98.61	92.97	87.93
D-Cysteine	98.61	93.45	87.66
Phenol	98.61	94.44	87.88
Albumin	98.61	94.44	89.39

[281] The degradation of Ac-225-DOTATATE in pure WFI was found significant even at the most diluted concentration for bolus injection.

Example 3. Control formulation without excipient

[282] The reaction mixture described in example 1 was immediately diluted to 50 x fold of volume with water for injection (WFI) or to 0.02 mCi/ml. pH was tested to be 6.13. The mixture was kept at room temperature (25°C). At different time points, purity of [^{225}Ac]Ac-DOTA-TATE in the formulated dose were measured by radio-TLC as described in the Table 7 below:

Table 7

Time after formulation (hours)	Percentage of ^{225}Ac present in [^{225}Ac]Ac-DOTA-TATE	Notes
0 hour	99.5%	0.5% free Actinium
24 hours	94.8%	2.0% free Actinium, 3.2% fragments
48 hours	91.8%	3.5% free Actinium, 4.8% fragments
72 hours	83.5%	8.8% free Actinium, 7.7% fragments
96 hours	79.1%	9.2% free Actinium, 11.8% fragments

Example 4. Radioactivity concentration optimization

[283] The reaction mixture described in example 1 was immediately diluted into Sodium Ascorbate (100 mM or 19.8 mg/ml aqueous solution, pH adjusted to 5.80) aqueous solution at different concentrations; DTPA was added into the formulation accordingly to reach the final concentration at 0.05 mg/ml. The mixture was kept at room temperature (25°C) and protected from light to prevent photodegradation. At different time points, purity of [^{225}Ac]Ac-DOTA-TATE in the formulated dose were measured by radio-TLC as described in the Table 8 below:

Table 8

	Percentage of ^{225}Ac present in [^{225}Ac]Ac-DOTA-TATE					
Radioactivity concentration	0 hour	24 hours	48 hours	72 hours	96 hours	120 hours
15 $\mu\text{Ci/ml}$	99.37	96.92	96.08	98.74	94.83	93.49
32 $\mu\text{Ci/ml}$	99.39	97.92	97.13	95.31	92.52	85.90
68 $\mu\text{Ci/ml}$	99.06	98.22	95.93	95.36	86.92	n/a
126 $\mu\text{Ci/ml}$	99.11	95.77	84.99	n/a	n/a	n/a
301 $\mu\text{Ci/ml}$	99.09	97.53	88.78	n/a	n/a	n/a
550 $\mu\text{Ci/ml}$	98.87	97.04	85.63	n/a	n/a	n/a

Example 5. DTPA concentration optimization

[284] The reaction mixture described in example 1 was immediately diluted to 50 x fold of volume (or to 20 $\mu\text{Ci/ml}$) with Sodium Ascorbate (100 mM or 19.8 mg/ml aqueous solution, pH adjusted to 5.80) aqueous solution. Different concentrations of DTPA were added. The mixture was kept at room temperature (25°C). At different time points, radioactive components of the formulated dose were measured by radio-TLC as described in the Table 9 below:

Table 9

	Percentage of ^{225}Ac present in [^{225}Ac]Ac-DOTA-TATE			
DTPA concentration	0 hour	24 hours	48 hours	72 hours
0.05 mg/ml	98.74	97.67	95.34	94.62
0.1 mg/ml	97.52	98.30	96.74	94.36
0.3 mg/ml	98.06	97.19	96.11	93.60
0.5 mg/ml	98.40	97.28	95.07	92.73
0.8 mg/ml	98.02	97.60	96.57	93.11
1.0 mg/ml	98.25	97.37	96.14	94.14

Example 6. Sodium ascorbate concentration optimization

[285] The reaction mixture described in example 1 was immediately diluted to 50 x fold of volume (or to 0.02 mCi/ml) with sodium ascorbate (100 mM, pH adjusted, with 0.05 mg/ml DTPA). pH was tested to be 5.83. The mixture was kept at room temperature (25°C). At different time points, radioactive components of the formulated dose were measured by radio-TLC as described in the Table 10 below:

Table 10

	Percentage of ^{225}Ac present in [^{225}Ac]Ac-DOTA-TATE						
Sodium ascorbate concentration	0 hour	24 hours	48 hours	72 hours	96 hours	120 hours	144 hours
200 mM	99.22	98.16	97.12	95.63	95.51	94.38	91.27
100 mM	99.15	98.76	96.94	96.16	95.84	95.44	95.34
10 mM*	99.78	92.21	86.11	n/a	n/a	n/a	n/a
1 mM*	99.76	91.11	52.06	n/a	n/a	n/a	n/a

* Radioactivity concentration at 1 mCi/ml

Example 7. Dextran ratio optimization

[286] The reaction mixture described in example 1 was immediately diluted to 40 x fold of volume (or to 25 $\mu\text{Ci/ml}$) with sodium ascorbate (100 mM, pH adjusted, with 0.05 mg/ml DTPA) in pre-mixed dextran saline solution. pH was tested to be 5.80. The mixture was kept at room temperature (25°C). At different time points, radioactive components of the formulated dose were measured by radio-TLC as described in the Table 11 below:

Table 11

	Percentage of ^{225}Ac present in [^{225}Ac]Ac-DOTA-TATE						
Dextran percentage	0 hour	24 hours	48 hours	72 hours	96 hours	120 hours	144 hours
10% w/w	99.67	99.02	98.75	97.83	96.42	96.58	95.37
6 % w/w	100	99.08	98.83	98.29	96.99	97.00	96.41
3% w/w	99.86	98.62	98.48	97.91	96.48	96.67	95.77
0% w/w	99.90	99.42	98.73	97.77	97.13	98.09*	94.64
10% w/w, no L-ascorbate	100	95.38	93.36	89.11	87.20	n/a	n/a

* non-homogeneous sampling

Example 8. EGCg concentration

[287] The reaction mixture described in example 1 was immediately diluted to 40 x fold of volume (or to 25 $\mu\text{Ci/ml}$) with sodium ascorbate (100 mM, pH adjusted 5.80, with 0.05 mg/ml DTPA) in saline solution with different concentration of EGCg. The mixture was kept at room temperature (25°C). At different time points, radioactive components of the formulated dose were measured by radio-TLC as described in the Table 12 below:

Table 12

	Percentage of ^{225}Ac present in ^{225}Ac Ac-DOTA-TATE						
EGCg concentration	0 hour	24 hours	48 hours	72 hours	96 hours	120 hours	144 hours
3 mg/ml	99.81	98.57	98.00	96.55	96.42	96.05	90.71
1 mg/ml	99.76	99.14	98.83	98.04	97.15	94.82	95.65
0.5 mg/ml	99.61	98.92	98.48	97.97	96.44	95.65	93.04
0 mg/ml	99.90	99.42	98.73	97.77	97.13	98.09*	94.64

*non-homogeneous sampling

Example 9. A preparation of ^{225}Ac Ac-DOTA-TATE at a single patient dose scale, its formulation and stability study

[288] For a 300 μCi (11.1 MBq) batch size, a ^{225}Ac Ac(NO₃)₃ solution (40 μl , 11.4 MBq, assayed) was diluted with sodium acetate buffer solution (250 μl , 0.4 M, pH = 5.50). The DOTA-TATE acetate solution (200 μl , 1.0 mg/ml water solution, 200 μg) was added. The mixture was mixed with vortex mixture, then heated at 90°C for 15 min at shaking speed of 500 round per minute on a thermal mixer. After completion, the reaction was removed from the mixture and allowed to cool to room temperature in 3 minutes. The reaction solution was diluted with pre-mixed intravenous formulation (9.5 ml). The Actinium-225 radioactive contains concentration was 30 mCi/L (total volume 10.0 ml). The calculated 5-day dose activity was 211 μCi (7.8 MBq, or 7.4MBq $\pm$ 10%). The starting molar activity of the dose was 2.2 mCi/ μmol . The formulated product was dispensed into a 30-ml sterile vial and sealed with Wheaton's septa and crimp seal. The vial was wrapped with aluminum foil and stored away from light at room temperature (about 20°C to about 25°C) for stability sampling every 24 hours. Intravenous formulation is either Formulation A or Formulation B as described below.

Formulation A:

To prepare a 100 grams of 100 mM sodium L-ascorbate, 5% w/w Dextran 40, 0.9% w/w sodium chloride saline solution, pH 5.80, 5.000 g of DEXTRAN 40, 1.980g of Sodium L-ascorbate and 5.0 mg of DTPA were dissolved in 93 ml of 0.9% w/w saline. The solution container was placed on a vortex shaker and mixed for 15 minutes to completely dissolve the solid. 24 μl of HCl (conc. 12 M) was added. Final pH was measured to between 5.75-5.85. The formulation solution was stored at 2-8 °C and protected from exposure of light up to 12 hours before consumption.

Formulation B:

To prepare 250 ml of a 100 mM sodium L-ascorbate, 0.9% w/w sodium chloride saline solution, pH 5.80, 4.950 g of Sodium L-ascorbate and 12.5 mg of DTPA were dissolved in 250 ml of 0.9% w/w saline. The solution container was placed on a vortex shaker and mixed for 15 minutes to

completely dissolve the solid. 60 µl of HCl (conc. 12 M) was added. Final pH was measured to between 5.75-5.85. The formulation solution was stored at 2-8 °C and protected from exposure of light up to 12 hours before consumption.

[289] At different time points, percentage purity of [^{225}Ac]Ac-DOTA-TATE in the formulated dose were measured by radio-TLC as described in the Table 13 below. Purity is described as the ^{225}Ac present in [^{225}Ac]Ac-DOTA-TATE divided by total ^{225}Ac content at that time point.

Table 13

Formulation	Percentage of ^{225}Ac present in [^{225}Ac]Ac-DOTA-TATE								
	0 hour	24 hours	48 hours	72 hours	96 hours	120 hours	144 hours	168 hours	192 hours
A	98.75	98.86	98.40	98.29	96.88	96.14	95.92	94.77	94.67
B	98.41	98.67	98.34	97.67	96.22	96.22	95.24	94.35	93.52

[290] As illustrated in the table above, both Formulations A and B retain at least 95 % of the ^{225}Ac content as ^{225}Ac -DOTA-TATE after 120 hours and at least 93% of the ^{225}Ac content as ^{225}Ac -DOTA-TATE after 192 hours.

[291] Example 10. Preparation of [^{225}Ac]Ac-DOTA-TATE for *in vivo* administration

[292] [^{225}Ac]Ac(NO₃)₃ was dissolved in 0.001M HCl to achieve a concentration of 1mCi in 100µL. A 1.0-1.1 mCi aliquot of 10 µCi/µL ^{225}Ac -chloride solution was combined with 285 µg of 1µg/µL DOTA-TATE solution in 0.4M sodium acetate buffer. The combined solution was brought to 2.0mL with 0.4M sodium acetate buffer and a final pH range of 6.0 to 6.5. The radioactive concentration of the combined solution was between 0.5mCi/mL and 0.55mCi/mL. The solution was heated and mixed with a thermal mixer at 90±3°C for 15±2 minutes. To a separate, sterile, intermediary vial was added 28mL of formulation buffer (100mM sodium ascorbate, 0.05mg/mL DTPA, 0.9% normal saline). The total contents of the combined [^{225}Ac]Ac-DOTA-TATE solution was transferred into the intermediary vial with the formulation buffer, further reducing the total radioactive concentration to 0.033-0.0367 mCi/mL in the formulation vial.

[293] The required volume to fill to the requested patient activity dose is calculated with appropriate decay factor to time of calibration and dose range between 146-275 µCi. If necessary, after activity has been aliquoted to the patient vial, the vial is brought to a total volume of 12mL with formulation buffer (100mM sodium ascorbate, 0.05mg/mL DTPA, 0.9% normal saline) for injection. Final excipient description [^{225}Ac]Ac-DOTA-TATE for *in vivo* administration was formulated in a sodium ascorbate concentration of 18.5±4.63 mg/mL, total DOTA-TATE peptide concentration of ≤11.5 µg/mL, 0.05 mg/mL DTPA, 0.9% normal saline, pH=5.5-7.0, with a dose range of 146-275 µCi at time of calibration in 12 mL total volume, and dose concentration at time

of calibration between 0.012 – 0.023 $\mu\text{Ci}/\mu\text{L}$. Stability up to 120 hours was initially verified with the bulk formulated vial and subsequently with the dose range between 146–275 μCi .

Example 11. Preparation of ^{225}Ac -DOTA-TATE formulation in unit dosage form

[294] The unit dosage form formulation was manufactured in a continuous process from radiolabeling of ^{225}Ac into the DOTA moiety of DOTATATE, to the final formulation with excipients. The unlabeled precursor DOTATATE was a lyophilized powder that was reconstituted in sodium acetate buffer prior to labeling with ^{225}Ac . DOTATATE acetate was labeled with ^{229}Th (thorium-229)-generator-derived ^{225}Ac under a specified temperature and reaction time to produce ^{225}Ac -DOTATATE. After radiolabeling was completed, the reaction mixture was further formulated in a buffer with selected excipients deemed necessary to mitigate radiolysis and breakdown of the drug product:

- 18.5 mg/mL L-sodium ascorbate (e.g., to mitigate radiolysis of the radiopharmaceutical preparation and extend stability)
- 0.05 mg/mL diethylenetriamine pentaacetate (e.g., to scavenge free unbound ^{225}Ac)
- 0.9% normal saline (to further dilute to a total infusion volume of 12 mL)
- Other suitable excipients may also be used.

[295] Example 12. Clinical trial design and dosing schedule

[296] The clinical trial design is a Phase 1b/Phase 3 global, multicenter, randomized, controlled, open-label trial comparing treatment with [^{225}Ac]Ac-DOTA-TATE to standard of care therapy in subjects with inoperable, advanced, Grade 1-2, well-differentiated, somatostatin receptor positive (SSTR+) GEP-NETs that have progressed according to RECIST v.1.1 following prior treatment with ^{177}Lu -DOTA-TATE or ^{177}Lu -DOTA-TOC.

[297] Part 1 of the study is to determine the recommended Phase 3 dose (RP3D), with dose de-escalation/re-escalation rules based on the Bayesian optimal interval (BOIN) design (Liu and Yuan 2015; Yuan 2016). Six subjects are planned to be enrolled in 3 dose cohorts for a total of 18 subjects if all 3 dose levels are initiated. A cohort may be expanded e.g., to a maximum of 10 subjects. The starting dose of [^{225}Ac]Ac-DOTA-TATE will be 120 kBq/kg (3.2 $\mu\text{Ci}/\text{kg}$). Subjects will receive up to 4 cycles of [^{225}Ac]Ac-DOTA-TATE every 8 weeks. Dose de-escalation (between cohorts) and potential re-escalation will be decided based on the dose limiting toxicity rate observed during the first 56 days following the first administration of [^{225}Ac]Ac-DOTA-TATE. Concomitant IV amino acids (solution containing L-arginine and L-lysine) will be given with each [^{225}Ac]Ac-DOTA-TATE administration for renal protection, starting 30 minutes before the [^{225}Ac]Ac-DOTA-TATE infusion and continuing for a total of 4 hours.

[298] A representative dosing scheme for Part 1 is illustrated in FIG. 19.

[299] The Eligibility Criteria of the Part 1 study can include one or more of the following:

- Age ≥ 18
- Histologically proven, G1-3 well-differentiated GEP-NETs
- Ki-67 $\leq 55\%$
- Progressive GEP-NET based on RECIST v1.1 (centrally confirmed) following ^{177}Lu -DOTATATE or ^{177}Lu -DOTATOC
- RECIST v1.1 measurable SSTR+ disease within 4 weeks prior to dose (centrally confirmed; no SSTR-neg metastatic disease)
- CrCl ≥ 50 mL/min
- Subjects with p-NET have also received an additional non-SSA antineoplastic agent in addition to prior peptide receptor radionuclide therapy (PRRT)

[300] The end point of the Part 1 study can include one or more of the following:

Primary: Dose Limiting Toxicities (DLTs)

Secondary/exploratory:

- Recommended Phase 3 dose (RP3D)
- Safety
- objective response rate (ORR)
- PK

[301] Part 2 (randomized, controlled Phase 3) is to determine if treatment with ^{225}Ac Ac-DOTA-TATE prolongs progression free survival as assessed by blinded independent central review (BICR) (primary objective) and OS (key secondary objective) compared with standard of care therapy. A total of 210 subjects are planned for randomization at a 1:1 ratio to receive ^{225}Ac Ac-DOTA-TATE administered at the RP3D every 8 weeks for up to 4 cycles or standard of care therapy selected by the Investigator prior to randomization and given according to local labeling (standard of care options may include oral everolimus, oral sunitinib, high dose octreotide long-acting release (LAR), and high dose lanreotide). Following radiographic progressive disease confirmed by BICR, subjects randomized to the standard of care therapy group may be eligible to cross over and receive ^{225}Ac Ac-DOTA-TATE.

[302] Pharmacokinetic evaluations of ^{225}Ac Ac-DOTA-TATE in blood and urine will be completed in Part 1 of the study (all subjects) and in a subset of subjects randomized to ^{225}Ac Ac-DOTA-TATE in Part 2 of the study. In addition, a PK/ECG substudy will be conducted in a subset of subjects

randomized to ^{225}Ac Ac-DOTA-TATE during Part 2.

[303] The Eligibility Criteria of the Part 2 study can include one or more of the following:

- Age ≥ 18
- Histologically proven, well-differentiated, G1-2 GEP-NETs

- $Ki-67 \leq 20\%$
- Progressive GEP-NET based on RECIST v.1.1 (centrally confirmed) following ^{177}Lu -DOTATATE or ^{177}Lu -DOTATOC
- RECIST v1.1 measurable SSTR+ disease within 4 weeks prior to dose (centrally confirmed; no RECIST measurable SSTR-neg metastatic disease)
- $\text{ECOG} \leq 2$
- $\text{CrCl} \geq 50 \text{ mL/min}$

[304] The end point of the Part 2 study can include one or more of the following:

Primary: blinded independent central review (BICR) progression-free survival (PFS)

Secondary/exploratory:

- overall survival (OS)
- objective response rate (ORR)
- duration of Response
- Disease Control Rate
- Safety
- PK
- Biomarkers
- QOL

[305] Example 13: Preparation of ^{225}Ac Ac-DOTA-TATE at a 1 mCi batch size, its formulation and stability study

[306] For a 1 mCi (37 MBq) batch size, a ^{225}Ac Ac(NO_3)₃ solution (93 μL , 995 μCi assayed) was diluted with sodium acetate buffer solution (1401 μL , 0.4M, pH=5.53). The DOTA-TATE acetate solution (285 μg , 0.964 $\mu\text{g}/\mu\text{L}$ sodium acetate buffer, 296 μL) was added for a molar activity of 5.009 Ci/mmol. The target reaction radioactive concentration was 0.556 $\mu\text{Ci}/\mu\text{L}$ with a total reaction volume of 1,789 μL . The mixture was mixed with a vortexer, then heated at 90°C for 15 minutes at shaking speed of 500 rounds per minute on a thermal mixer. After completion, the reaction vial was removed from the thermal mixer and cooled to room temperature (about 20°C to about 25°C) in 3 minutes. The entire reaction mixture was then added to 28.2 mL of a pre-mixed formulation buffer (Formulation B) consisting of 100 mM sodium L-ascorbate, 0.05 mg/mL DTPA in 0.9% saline (pH = 5.79). The final assay of the bulk vial solution was 984 μCi in a total volume of 30,000 μL , for a final product radioactive concentration of 0.033 $\mu\text{Ci}/\mu\text{L}$ and final pH of 5.67. A total of 3 aliquots from the bulk vial was distributed to 3 separate vials, simulating patient dose activity levels of 307.5 μCi in 9 mL, 309.5 μCi in 9 mL, and 310 μCi in 9 mL. Each of the simulated patient vial was protected from light and stored in room temperature

(20-25°C). Stability sampling was taken every 24 hours from the 309.5 μCi vial, with an end specification of $\geq 95\%$ by $t=120$ hours from end of synthesis.

[307] At different time points, percentage purity of [^{225}Ac]Ac-DOTA-TATE in the formulated dose were measured by radio-TLC as described in the Table 14 below. Purity is described as the ^{225}Ac present in [^{225}Ac]Ac-DOTA-TATE divided by total ^{225}Ac content at that time point.

Table 14

	Percentage of ^{225}Ac present in [^{225}Ac]Ac-DOTA-TATE						
	0 hour	24 hours	48 hours	72 hours	96 hours	120 hours	144 hours
1 mCi Formulation	99.21%	98.87%	97.21%	96.54%	Not measured	95.52%	94.81%

[308] As illustrated in the table above, the formulation of Example 13 retains at least 95 % of the ^{225}Ac content as ^{225}Ac -DOTA-TATE after 120 hours.

[309] Example 14: [^{225}Ac]Ac-DOTA-TATE dosing calculation based on patient weight

[310] An 85kg patient is treated with a dose of 3.24 $\mu\text{Ci/kg}$ (120 kBq/kg) [^{225}Ac]Ac-DOTA-TATE representing a total radiation dose of 275 μCi (10,200kBq) at time of injection. The final product after synthesis and formulation has a radioactive concentration of 0.033 $\mu\text{Ci}/\mu\text{L}$. Given the half-life of ^{225}Ac , the dose is formulated to contain a certain amount of radioactivity dependent upon when the dose will be administered according to the following Table 15:

Table 15

	Days before administration				
	1	2	3	4	5
μCi in radiopharmaceutical	295	317	340	364	391
Volume of radiopharmaceutical (mL)	8.9	9.6	10.3	11.0	11.8

The dose is then brought up to 12mL total volume with formulation buffer for administration. Patients less than 85kg receive the same 3.24 $\mu\text{Ci/kg}$ (120 kBq/kg) dose of [^{225}Ac]Ac-DOTA-TATE brought up to 12mL total volume with formulation buffer for administration.

[311] Further, the Table 16 below summaries the dose calculation for patients having different weights at a dose of 120 kBq/kg:

Table 16

Patent weight (kg)	40	45	50	55	60	65	70	75	80	85
Dose at time of injection (in μCi)	130	146	162	178	194	211	227	243	259	275
Dose at time of injection (in kBq)	4800	5400	6000	6600	7200	7800	8400	9000	9600	10200
Days before administration	Activity needed (in μCi) at day of manufacture if injected x days later									
1	139	156	174	191	208	226	243	261	278	295
2	149	168	186	205	224	242	261	279	298	317
3	160	180	200	220	240	260	280	300	320	340
4	171	193	214	236	257	278	300	321	343	364
5	184	207	230	253	276	299	322	345	368	391
Days before administration	Volume needed (in mL) if bulk drug product concentration = 0.033 $\mu\text{Ci}/\mu\text{L}$									
1	4.2	4.7	5.3	5.8	6.3	6.8	7.4	7.9	8.4	8.9
2	4.5	5.1	5.6	6.2	6.8	7.3	7.9	8.5	9.0	9.6
3	4.8	5.4	6.1	6.7	7.3	7.9	8.5	9.1	9.7	10.3
4	5.2	5.8	6.5	7.1	7.8	8.4	9.1	9.7	10.4	11.0
5	5.6	6.3	7.0	7.7	8.4	9.0	9.7	10.4	11.1	11.8

[312] Example 15: Biopsy classification and H-Score calculation

[313] Tissue biopsies were collected and stained to detect SSTR2 expression. Tissue samples were classified as SSTR2 positive based on their H-Score. An H-Score of 10 or greater is indicative of positive expression. An H-Score of 100 or greater is indicative of tissues with high SSTR2 expression. Staining intensity is graded as 0, 1, 2, or 3 (for negative, weak, moderate, and strong) and the percentage of cells in each group is recorded. The H-score is obtained using the formula: $\text{H-Score} = (1 \times \% \text{ of cells stained at intensity category 1}) + (2 \times \% \text{ of cells stained at intensity category 2}) + (3 \times \% \text{ of cells stained at intensity category 3})$. Analysis of 70 SCLC tumors revealed 47% of SCLC tumors express SSTR2 with 27% of SCLC tumors categorized with high expression (i.e., H-score higher than 100). SCLC samples and their H-score

classification are provided in the following Table 17:

Table 17

% of Samples	H-Score
53	0-10 (negative)
20	11-100
16	101-200
11	201-300

[314] Figures 20A and 20B illustrate representative stained tissue examples.

[315] Example 16. Part 1 Study of [^{225}Ac]Ac-DOTA-TATE in Combination with Platinum + Etoposide + PD-L1 inhibitor for Untreated (1L) SSTR+ ES-SCLC

[316] Part 1 of the study is to determine the recommended Phase 2 dose (RP2D), with dose escalation, in combination with standard of care therapy (SoC) comprising a platinum agent (e.g. carboplatin or cisplatin), etoposide, and a PD-L1i (e.g. durvalumab or atezolizumab) in untreated subjects with SSTR + ES-SCLC. The study will evaluate safety and tolerability of [^{225}Ac]Ac-DOTA-TATE using a standard 3+3 design. Three to six subjects are planned to be enrolled in each dose cohort. If no dose-limiting toxicities (DLTs) are observed among 3 subjects following the first dose, then the dose will be escalated to the next higher level. The starting dose of [^{225}Ac]Ac-DOTA-TATE will be 175 μCi . Dose escalation will continue until at least 2 subjects among a cohort of 3-6 subjects experience a DLT, or until a maximum activity level of 275 μCi . If ≥ 2 of 6 subjects experience a DLT, the dose will be de-escalated to 125 μCi . Subjects will receive [^{225}Ac]Ac-DOTA-TATE administered by IV infusion every 4-6 weeks for a maximum of 6 infusions. Concomitant IV amino acids (solution containing L-arginine and L-lysine) will be given with each [^{225}Ac]Ac-DOTA-TATE administration for renal protection, starting 30 minutes before the [^{225}Ac]Ac-DOTA-TATE infusion and continuing for a total of 4 hours. [^{225}Ac]Ac-DOTA-TATE is administered on the same day or up to two days before administration of PD-L1i, Platinum (C), and Etoposide (E). The PD-L1i (e.g. durvalumab or atezolizumab), platinum agent, and Etoposide are administered at standard of care dosages. The PD-L1i (e.g. durvalumab 1,500 mg) is given for a total of 4 cycles followed by maintenance dosing on day 1 every 28 days. Alternatively, the PD-L1i (e.g. atezolizumab 840mg, 1,200mg, or 1,680mg) is given for a total of 4 cycles followed by maintenance dosing on day 1 every 14 (at 840mg), 21 (at 1,200mg), or 28 (at 1,680mg) days. The platinum (carboplatin at 5-6AUC or cisplatin at 75-80mg/m²) is given on day 1 of each 21-day cycle for a maximum total of 4 cycles. The etoposide is given at 80-100mg/m² on days 1, 2, and 3 of each 21- day cycle for a maximum total of 4 cycles. When the atezolizumab is the PD-L1i, then carboplatin is used as the platinum agent.

[317] A representative dosing scheme is provided in FIG. 21.

[318] The Eligibility Criteria for the Part 1 study can include one or more of the following:

- Age ≥ 18
- Histologically or cytologically proven ES-SCLC
- Untreated or received ≤ 1 cycle of platinum-etoposide and PD-L1 inhibitor therapy. If ≤ 1 cycle treatment with platinum-etoposide and PD-L1 inhibitor:
 - ≥ 1 SSTR+ RECIST v1.1 measurable site of disease; $\geq 50\%$ of measurable lesions must be SSTR+
- CrCl ≥ 50 mL/min (≥ 60 mL/min with cisplatin)
- Adequate bone marrow function: ANC $\geq 1000/\text{mm}^3$; Platelets $\geq 50,000/\text{m}^3$; HgB ≥ 8 g/dL
- ECOG ≤ 1
- Brain mets asx or on stable or decreasing dose regimen of steroids
- No prior XRT to chest or planned consolidation chest XRT or prior XRT to $> 25\%$ bone marrow

[319] The end point of the Part 1 study can include one or more of the following:

Primary: Dose Limiting Toxicities (DLTs)

Secondary/exploratory:

- Recommended Phase 2 dose (RP2D)
- Safety
- objective response rate (ORR)
- PK

[320] **Example 17.** Part 2 Study of [^{225}Ac]Ac-DOTA-TATE in Combination with Platinum + Etoposide + PD-L1 inhibitor for Untreated (1L) or Platinum-sensitive Refractory (2L or second line) SSTR+ ES-SCLC

[321] Part 2 of the study is to determine the efficacy, safety and tolerability of [^{225}Ac]Ac-DOTA-TATE at the RP2D determined in Part 1 in combination with SoC, separately in subjects with 1L-ES-SCLC and subjects with 2L-ES-SCLC. A Simon 2-stage design will be utilized to determine expansion of each cohort, and the 2L-ES-SCLC cohort will be considered for further expansion into a registrational cohort. Up to 60 subjects across both cohorts (if both cohorts are expanded in the second stage of the Simon 2-stage design) will be enrolled. Concomitant IV amino acids (solution containing L-arginine and L-lysine) will be given with each [^{225}Ac]Ac-DOTA-TATE administration for renal protection, starting 30 minutes before the [^{225}Ac]Ac-DOTA-TATE infusion and continuing for a total of 4 hours.

[322] The 1L-ES-SCLC cohort (untreated) will receive [^{225}Ac]Ac-DOTA-TATE by IV infusion

at the RP2D once every 4 or 6 weeks (every 6 weeks during SoC therapy and every 4 weeks during PD-L1 inhibitor maintenance phase) for a maximum of 6 infusions plus SoC of platinum (carboplatin at 5-6AUC or cisplatin at 75-80mg/m²), etoposide (80-100mg/m²), and PD-L1 inhibitor (e.g. durvalumab 1,500mg) infusions every 3 weeks for a total of 4 × 21-day cycles, followed by maintenance PD-L1 inhibitor administration once every 4 weeks. Alternatively, the PD-L1 inhibitor (e.g. atezolizumab 840mg, 1,200mg, or 1,680mg) is given by infusion every 2, 3, or 4 weeks for a total of 4 x 14 (at 840mg), 4 x 21 (at 1200mg), or 4 x 28 (at 1680mg) day cycles, followed by maintenance PD-L1 inhibitor administration on day 1 every 14 (at 840mg), 21 (at 1,200mg), or 28 (at 1,680mg) days. When the atezolizumab is the PD-L1i, then carboplatin is used as the platinum agent.

[323] The 2L-ES-SCLC cohort (platinum sensitive, refractory): will receive [²²⁵Ac]Ac-DOTA-TATE at the RP2D once every 4 or 6 weeks (every 6 weeks during SoC therapy and every 4 weeks thereafter) for a maximum of 6 infusions plus SoC of platinum and etoposide infusions administered every 3 weeks for a total of 4 × 21-day cycles.

[324] An exemplary clinical trial design is provided in FIG. 22.

[325] The Eligibility Criteria for the Part 2 study can include one or more of the following:

- Age ≥ 18
- Histologically or cytologically proven ES-SCLC (1L Cohort)
- Histologically or cytologically proven, relapsed or refractory ES-SCLC (2L cohort)
- 1L cohort: untreated or received ≤ 1 cycle of platinum-etoposide and PD-L1 inhibitor therapy (and same criteria Phase 1b)
- 2L cohort: progressive ≥ 90 days following 1 prior platinum-containing regimen
- ≥ 1 SSTR+ RECIST v1.1 measurable site of disease; ≥50% of measurable lesions must be SSTR+
- CrCl ≥ 50 mL/min (≥ 60 mL/min with cisplatin)
- Adequate bone marrow function: ANC ≥ 1000/mm³; Platelets ≥ 50,000/m³; Hgb ≥ 8 g/dL
- ECOG ≤ 1
- No prior XRT to > 25% bone marrow
- 1L Cohort: no prior XRT to chest or planned consolidation chest XRT
- 2L Cohort: prior radiotherapy to the chest must be completed > 6 weeks and prophylactic cranial radiation must be completed >2 weeks from first dose of study medication

[326] The end point of the Part 2 study can include one or more of the following:

Primary:

- 1L Cohort: durable response (% with duration of response ≥4 mo)
- 2L Cohort: objective response rate

Secondary/exploratory:

- Duration of response
- Progression free survival
- Overall survival
- Objective response rate (1L)
- Disease control rate
- Safety
- Biomarkers, including but not limited to expression of SSTR2, PD-L1, Rb, TP53, ASCL1, NEUROD1, POU2F3, and CD8 expression, baseline SUV_{max}
- PK
- European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30
- European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13)

[327] Example 18. Additional Study Designs

[328] This is a global, multicenter, single arm, open-label, 2-part (Part 1 [Phase 1b] followed by Part 2 [Phase 2]) study of [²²⁵Ac]Ac-DOTA-TATE for injection in combination with SoC consisting of platinum (carboplatin or cisplatin) + etoposide +/- PD-L1 inhibitor (durvalumab or atezolizumab) in subjects with ES-SCLC. Safety and efficacy of [²²⁵Ac]Ac-DOTA-TATE in combination with SoC will be evaluated, and pharmacokinetics (PK) of [²²⁵Ac]Ac-DOTA-TATE will be assessed.

[329] Part 1 is the dose escalation portion of the study to evaluate safety and determine the RP2D of [²²⁵Ac]Ac-DOTA-TATE in combination with SoC therapy (platinum + etoposide + PD-L1 inhibitor) using a standard 3 + 3 design in subjects with untreated SSTR+ ES-SCLC (1L-ES-SCLC). The initial dose of [²²⁵Ac]Ac-DOTA-TATE will be one dose level below the monotherapy dose evaluated in studies of ²²⁵Ac-DOTATATE in GEP-NETs (see Example 12). SoC consisting of platinum + etoposide + PD-L1 inhibitor will be administered at standard doses recommended for primary treatment of ES-SCLC.

[330] Part 2 is the open-label, expansion cohort portion of the study to evaluate the efficacy and safety of [²²⁵Ac]Ac-DOTA-TATE at the R2PD (determined in Part 1) in combination with SoC in

- (1) subjects with untreated SSTR+ ES-SCLC (1L-ES-SCLC cohort) and
- (2) subjects with platinum-sensitive ES-SCLC defined as PD ≥90 days following 1 prior platinum-containing regimen (2L-ES-SCLC cohort)

[331] In Part 2, all subjects will receive [²²⁵Ac]Ac-DOTA-TATE at the RP2D plus SoC

consisting of platinum + etoposide + PD-L1 inhibitor (1L-ES-SCLC cohort) or SoC consisting of platinum + etoposide (2L-ES-SCLC cohort). This portion of the study will utilize a Simon 2-stage design (Simon 1989) to determine expansion of each cohort. The 2L-ES-SCLC cohort will be considered for further expansion into a registrational cohort.

[332] After providing informed consent, all subjects (Part 1 and Part 2) will undergo screening assessments to determine eligibility for participation in the study. Subjects who meet all eligibility criteria will be enrolled. The screening period for the study will be up to 28 days (Day -28 to -1), and eligible subjects will receive their first dose of [²²⁵Ac]Ac-DOTA-TATE on Day 1 (window of +7 days after initiation of SoC therapy is allowed). Note: Subjects in the 1L-ES-SCLC cohort in Part 1 or Part 2 may receive their first dose SoC therapy (i.e., Cycle 1) during the screening period and will receive their first dose of [²²⁵Ac]Ac-DOTA-TATE on Day 1, within 7 days of SoC Cycle 2.

[333] Safety and efficacy will be assessed at study visits as detailed in the SOAs for Part 1 and Part 2. During the treatment period, subjects in Part 1 and Part 2 will be radiographically evaluated every 6 or 8 weeks for disease progression and tumor response using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Subjects who complete the study or develop PD will be followed approximately every 3 months (via phone or office visit) for survival status, AEs/ SAEs considered to be related [²²⁵Ac]Ac-DOTA-TATE, adverse events of special interest (AESIs), laboratory evaluations (may be completed locally), development of secondary malignancy, and new anticancer therapy information until the end of the study (i.e., LTFU). PK parameters for [²²⁵Ac]Ac-DOTA-TATE will be evaluated.

[334] A schema of the overall study design is provided FIG. 21 (Part 1) and FIG. 22 (Part 2).

[335] Example 18-A. Part 1: Dose Escalation

[336] Part 1 will evaluate safety and tolerability of [²²⁵Ac]Ac-DOTA-TATE and determine the RP2D of [²²⁵Ac]Ac-DOTA-TATE with dose escalation/de-escalation rules using a standard 3+3 design. Three subjects are planned to be enrolled in each dose cohort. If no dose-limiting toxicities (DLTs) are observed among 3 subjects in the first 6 weeks, then the dose will be escalated to the next higher level. If 1 DLT is observed among 3 subjects in the first 6 weeks, then 3 additional subjects will be enrolled at the same dose level. If no additional subjects experience a DLT, the dose will be escalated to the next higher level. Dose escalation will continue until at least 2 subjects among a cohort of 3 to 6 subjects experience a DLT or until the maximum activity level of 275 μ Ci is reached. If ≥ 2 of 6 subjects experience a DLT in the first 6 weeks at any dose level, then the next lower dose level will be considered the maximum tolerated dose (MTD) or RP2D, assuming at least 6 subjects are treated with at least 1 infusion of [²²⁵Ac]Ac-DOTA-TATE at that dose level. If ≥ 2 of 6 subjects experience a DLT at Dose Level 1 in the first 6 weeks, the dose will

be de-escalated. (To further characterize the MTD/RP2D, 12 additional subjects may be enrolled in Part 1 to add to any of the planned doses or to test intermediate doses.)

[337] Subjects will receive up to 6 doses of [²²⁵Ac]Ac-DOTA-TATE plus up to 4 × 21-day cycles of SoC therapy consisting of platinum + etoposide + PD-L1 inhibitor followed by PD-L1 inhibitor maintenance as follows:

[338] [²²⁵Ac]Ac-DOTA-TATE will be administered by IV infusion once every 4 or 6 weeks (every 6 weeks during SoC therapy and every 4 weeks during PD-L1 maintenance phase) for a maximum of 6 infusions.

[339] SoC therapy will be administered by IV infusion every 3 weeks for a total of 4 × 21-day cycles, followed by maintenance PD-L1 inhibitor administration once every 4 weeks until PD (PD-L1 inhibitor maintenance phase). Note: Subjects may receive their first cycle of SoC therapy during the 28-day screening period.

[340] SoC will be administered at standard doses recommended for primary treatment of ES-SCLC and will not vary, except as needed for SoC treatment-specific dose modification.

[341] Starting dose and dose escalation levels for [²²⁵Ac]Ac-DOTA-TATE are provided in Table 18. The [²²⁵Ac]Ac-DOTA-TATE starting dose is 175 µCi (Dose Level 1). If Dose Levels 1 and 2 (225 µCi) are tolerated, the dose of [²²⁵Ac]Ac-DOTA-TATE may be escalated to a maximum of 275 µCi (Dose Level 3). If Dose Level 1 is not tolerated, the dose will be de-escalated to 125 µCi (Dose Level -1). Intermediate doses may be explored based on evaluation of all available data.

Table 18. Dose Escalation Cohorts

	Cohort	[²²⁵ Ac]Ac-DOTA-TATE Dose
Dose Level -1	-1	125 µCi
Dose Level 1	1	175 µCi
Dose Level 2	2	225 µCi
Dose Level 3	3	275 µCi

Note: Intermediate doses may be explored based on evaluation of all available data and recommendations from Data Review Committee. Dose Level 3 (275 µCi) is the maximum dose to be used in the study.

[342] Each dose escalation (between cohorts) and potential de-escalation step will be decided based on the DLT rate observed during the first 42 days following the first treatment with [²²⁵Ac]Ac-DOTA-TATE (DLT period) in the current dose cohort.

[343] **Example 18-B.** Part 2: Cohort Expansion

[344] Part 2 will evaluate the efficacy and safety and tolerability of [²²⁵Ac]Ac-DOTA-TATE at

the RP2D determined in Part 1 in combination with SoC, separately in subjects with 1L-ES-SCLC and subjects with 2L-ES-SCLC. A Simon 2-stage design will be utilized to determine expansion of each cohort, and the 2L-ES-SCLC cohort will be considered for further expansion into a registrational cohort. Approximately 60 subjects across both cohorts (if both cohorts are expanded in the second stage of the Simon 2-stage design) will be enrolled (see FIG. 22).

[345] [²²⁵Ac]Ac-DOTA-TATE and SoC will be administered as follows in Part 2:

- 1L-ES-SCLC cohort: Subjects will receive [²²⁵Ac]Ac-DOTA-TATE administered by IV infusion once every 4 or 6 weeks (every 6 weeks during SoC therapy and every 4 weeks during PD-L1 inhibitor maintenance phase) for a maximum of 6 infusions plus SoC consisting of platinum + etoposide + PD-L1 inhibitor infusions every 3 weeks for a total of 4 × 21-day cycles, followed by maintenance PD-L1 inhibitor administration once every 4 weeks until PD. Note: Subjects may receive their first cycle of SoC therapy during the 28-day screening period.
- 2L-ES-SCLC cohort: Subjects will receive [²²⁵Ac]Ac-DOTA-TATE administered by IV infusion once every 4 or 6 weeks (every 6 weeks during SoC therapy and every 4 weeks thereafter) for a maximum of 6 infusions plus SoC consisting of platinum + etoposide infusions administered every 3 weeks for a total of 4 × 21-day cycles.

[346] For each cohort in Part 2, 12 subjects will be enrolled at Simon Stage 1; if ≥4 of 12 subjects have a response (defined as durable response ≥4 months for 1L-ES-SCLC and defined as objective response [CR + PR] for 2L-ES-SCLC, Simon Stage 2 will be opened to enroll an additional 16 subjects per cohort. At the end of Stage 2, if ≥12 of 28 subjects respond, the [²²⁵Ac]Ac-DOTA-TATE treatment will be considered promising for further evaluation. For the 2L-ES-SCLC cohort this may include further expansion.

[347] Example 18-C. Inclusion Criteria

[348] The study population can consist of adult subjects with SSTR+-ES-SCLC who are untreated (1L-ES-SCLC; Part 1 and Part 2) or who progressed ≥90 days following 1 prior platinum-containing regimen (2L-ES-SCLC; Part 2).

[349] The inclusion criteria can include one or more of the following:

- Part 1 and Part 2, 1L-ES-SCLC cohort: Cytologically or histologically confirmed proven ES-SCLC (Stage IV [T any, N any, M 1a/b/c]) or T 3-4 due to multiple lung nodules or tumor/nodal volume that is not amenable to a tolerable radiation plan) and is untreated or received ≤1 cycle of platinum-etoposide and PD-L1 inhibitor therapy (including SoC administered during screening, if applicable)
- Part 2, 2L-ES-SCLC cohort: Cytologically or histologically confirmed relapsed or refractory proven ES-SCLC (Stage IV [T any, N any, M 1a/b/c]) or T 3-4 due to multiple

lung nodules or tumor/nodal volume that is not amenable to a tolerable radiation plan) and progressive ≥ 90 days following 1 prior platinum-containing regimen

- Subject is a candidate for therapy with SoC which includes:
 - a. Platinum (cisplatin or carboplatin) for a maximum of 4 cycles
 - b. Etoposide for a maximum of 4 cycles
 - c. PD-L1 inhibitor (Part 1 and Part 2, 1L-ES-SCLC cohort only) Eastern Cooperative Oncology Group (ECOG) PS 0-1
- Life expectancy of at least 12 weeks
- There must be at least 1 SSTR-positron emission tomography (PET) imaging-positive (using a regulatory agency-approved imaging method, e.g., 68Gallium, 64Copper), not previously irradiated, measurable site of disease (according to RECIST v1.1) and $\geq 50\%$ of RECIST v1.1 measurable metastatic lesions must be regulatory agency-approved SSTR imaging-positive (SSTR imaging-positive is defined as uptake greater than the liver uptake observed on regulatory agency-approved SSTR-PET imaging, i.e., Krenning score 3 or 4)
- Sufficient renal function, as evidenced by creatinine clearance (CrCl) ≥ 50 mL/min (≥ 60 mL/min with cisplatin) (calculated using the Cockcroft-Gault formula)
- Adequate hematologic function
- Adequate hepatic function

[350] Example 18-D. Exclusion Criteria

[351] The exclusion criteria can include one or more of the following:

- Part 1 and Part 2, 1L-ES-SCLC cohort only: Prior exposure to immune-mediated therapy, including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-PD-L2 antibodies, excluding anticancer vaccines and excluding 1 cycle of SoC therapy administered during the screening period.
- Part 1 and Part 2, 1L-ES-SCLC cohort only: Any condition requiring systemic treatment with immunosuppressive medications within 14 days prior to first dose of study medication (including >10 mg daily prednisone equivalents unless solely for the purpose of adrenal replacement). Inhaled or topical steroids or immunosuppressive medications, and single dose of steroids as pre-medication for CT scans with contrast are permitted.
- Part 1 and Part 2, 1L-ES-SCLC cohort only: Known active or suspected autoimmune disease, including paraneoplastic syndromes of autoimmune nature (except vitiligo, alopecia, type 1 diabetes mellitus, autoimmune hypothyroidism stable on hormone replacement, celiac disease stable on diet alone, psoriasis requiring only topical treatment. Other prior conditions not expected to recur should be discussed with the Medical Monitor).

- Prior PRRT.
- Known hypersensitivity to ^{225}Ac , ^{68}Ga , ^{64}Cu , octreotate, or any of the excipients of DOTATATE imaging agents
- Contraindication to receive platinum or etoposide.
- Prior radiotherapy as defined by:
- Part 1 and Part 2, 1L-ES-SCLC cohort: certain prior radiotherapy to the chest prior to systemic therapy or planned consolidation chest radiation therapy or prior external beam radiation therapy to more than 25% of the bone marrow.
- Part 2, 2L-ES-SCLC cohort: certain prior external beam radiation therapy to more than 25% of the bone marrow.
- Major surgery within 12 weeks prior to first dose of study drug.
- Part 2, 2L-ES-SCLC cohort: use of anticancer agents within the following intervals prior to the first dose of study drug: Chemotherapy: within <6 weeks; Small molecule inhibitors: within <4 weeks; or Biological agents: within <7 days or <5 half-lives, whichever is longer

[352] Example 18-E. Dosing regimen

[353] Exemplary dosing regimen under Example 18 is illustrated in Table 19 and Table 20 below:

Table 19. Study Intervention(s) Administered: 1L-ES-SCLC Subjects (Part 1 and Part 2)

Intervention Label	Investigational Product	Standard of Care Therapy
Intervention name	^{225}Ac Ac-DOTA-TATE	Standard of Care (SoC)
Dosage formulation	Injection	Injection
Unit dose strength(s)	kBq (μCi)	Carboplatin (AUC) Cisplatin (mg/m^2) Etoposide (mg/m^2) PD-L1i (mg)
Dosage level(s)	Part 1: Dose Level -1: 125 μCi Dose Level 1: 175 μCi Dose Level 2: 225 μCi Dose Level 3: 275 μCi Each dose level administered once every 4 or 6 weeks.	Part 1 and Part 2: <u>PD-L1i:</u> • Durvalumab: 1500 mg administered IV over 60 (+10) minutes on the first day of every 21-day cycle for a maximum of 4 $\times$ 21-day cycles, followed by once every 28 days (maintenance) or

Intervention Label	Investigational Product	Standard of Care Therapy
	<u>Part 2:</u> RP2D (selected in Part 1) administered once every 4 or 6 weeks	- Atezolizumab: 840/1200/1680 mg administered IV over 60 (+10) minutes on the first day of every 14/21/28-day cycle for a maximum of 4 cycles, followed by once every 14/21/28 days (maintenance) <u>Platinum:</u> - Carboplatin AUC 5-6 administered IV over 60 minutes on the first day of each 21-day cycle for a maximum of 4 × 21-day cycles or - Cisplatin 75-80 mg/m² IV over 60 minutes on the first day of each 21-day cycle for a maximum of 4 × 21-day cycles <u>Etoposide:</u> 80-100 mg/mm² administered IV over 60 minutes on 3 consecutive days starting on the first day of every 21-day cycle for a maximum of 4 × 21-day cycles. Infusion times and sequencing for platinum and etoposide may be adapted according to local standard-of-care.
Route of administration	IV infusion	IV infusion

Table 20. Study Intervention(s) Administered to 2L(second line)-ES-SCLC Subjects (Part 2)

Intervention Label	Investigational Product	Standard of Care Therapy
Intervention name	[²²⁵ Ac]Ac-DOTA-TATE	Standard of Care
Dosage formulation	Injection	Injection
Unit dose strength(s)	kBq (μCi)	Carboplatin (AUC) Cisplatin (mg/m ²)

		Etoposide (mg/m ²)
Dosage level(s)	RP2D (selected in Part 1) administered once every 4 or 6 weeks	<u>Platinum:</u> • Carboplatin AUC 5-6 administered IV over 60 minutes on the first day of each 21-day cycle for a maximum of 4 × 21-day cycles or • Cisplatin 75-80 mg/m² IV over 60 minutes on the first day of each 21-day cycle for a maximum of 4 × 21-day cycles <u>Etoposide:</u> 80-100 mg/mm² administered IV over 60 minutes on 3 consecutive days starting on the first day of every 21-day cycle for a maximum of 4 × 21-day cycles. Infusion times and sequencing for platinum and etoposide may be adapted according to local standard-of-care.
Route of administration	IV infusion	IV infusion

[354] Example 19. Preparation and *in vivo* efficacy of [²²⁵Ac]Ac-DOTA-TATE and [²²⁵Ac]Ac-DOTA-JR-11 in H727 mouse model

[355] A batch of [²²⁵Ac]Ac-DOTA-TATE and a batch of [²²⁵Ac]Ac-DOTA-JR-11 were produced to compare *in vivo* efficacy in H727 tumor model in mice. The study also aimed to determine if the buffering system and formulation for [²²⁵Ac]Ac-DOTA-TATE produced good radiolabeling yield as ascertained via radioTLC. For the [²²⁵Ac]Ac-DOTA-TATE preparation, 85.2 µCi of a [²²⁵Ac]Ac(NO₃)₃ solution (11.3 µl) was diluted with sodium acetate buffer solution (161 µl, 0.4 M, pH = 6.15). The DOTA-TATE acetate solution (24 µl, 1.0 mg/ml water solution, 24 µg) was added. The mixture was mixed with a vortexer, then heated at 90°C for 15 min at shaking speed of 500 round per minute on a thermal mixer. After completion, the reaction was removed from the mixture and allowed to cool to room temperature for 3 minutes. The reaction

solution was diluted with formulation buffer consisting of 100 mM sodium L-ascorbate, 0.05 mg/mL DTPA, and 0.9% saline (1934 μ L, pH=5.65). The Actinium-225 radioactive concentration was 40.9 mCi/L (total volume 2,130 μ L). The starting molar activity of the dose was 5.1 mCi/ μ mol. The formulated product was dispensed into a 5-ml sterile vial and sealed with Wheaton's septa and crimp seal.

[356] For the [^{225}Ac]Ac-DOTA-JR-11 preparation, 88.7 μ Ci of a [^{225}Ac]Ac(NO₃)₃ solution (11.3 μ L) was diluted with sodium acetate buffer solution (152 μ L, 0.4 M, pH = 6.15). The mixture was mixed with a vortexer, then heated at 90°C for 15 min at shaking speed of 500 round per minute on a thermal mixer. After completion, the reaction was removed from the mixture and allowed to cool to room temperature for 3 minutes. The reaction solution was diluted with formulation buffer consisting of 100 mM sodium L-ascorbate, 0.05 mg/mL DTPA, and 0.9% saline (2,021 μ L, pH=5.65). The Actinium-225 radioactive concentration was 39.0 mCi/L (total volume 2,218 μ L). The starting molar activity of the dose was 5.6 mCi/ μ mol. The formulated product was dispensed into a 5-ml sterile vial and sealed with Wheaton's septa and crimp seal.

[357] At different time points, percentage purity of [^{225}Ac]Ac-DOTA-TATE in the formulated dose were measured by radio-TLC as described in the Table 20 below. Purity is described as the ^{225}Ac present in [^{225}Ac]Ac-DOTA-TATE divided by total ^{225}Ac content at that time point. Only the t=0 time point was selected for analysis to ensure the mice were dosed in the appropriate timeframe.

Table 20.

	Percentage of ^{225}Ac present in [^{225}Ac]Ac-DOTA-TATE versus [^{225}Ac]Ac-JR-11 in the same formulation
Formulation	0 hour
[^{225}Ac]Ac-DOTA-TATE	98.10
[^{225}Ac]Ac-DOTA-JR-11	97.35

[358] As illustrated in the table above, both formulations were radiolabeled with at least 95% of the ^{225}Ac content as [^{225}Ac]Ac-DOTA-TATE and [^{225}Ac]Ac-DOTA-JR-11 at t=0 hours.

[359] After confirmation of the radioTLC results, mice for each group were selected to receive either 4 μ Ci of [^{225}Ac]Ac-DOTA-TATE (n=9) or 4 μ Ci of [^{225}Ac]Ac-DOTA-JR-11 (n=9). A vehicle group (n=9) was also used that were injected with ~100 μ L of only formulation buffer (100 mM sodium L-ascorbate, 0.05 mg/mL DTPA, and 0.9% saline) as control. Animals were weighed and tumors were sized for 24 days. The mean tumor volume is shown in Figure 23A and the mean body weight is shown in Figure 23B. As illustrated in FIG. 23A and FIG. 23B, both [^{225}Ac]Ac-DOTA-TATE and [^{225}Ac]Ac-DOTA-JR-11 showed similar efficacious results

compared to vehicle using the same buffer and formulation.

[360] Example 20. Exemplary Formulations

[361] Formulations of Tables 21A, 21B, and 21C are prepared with similar methods according to Example 9 and Example 19. The mixtures are kept at 20°C-25°C. At different time points, radioactive components of the formulated dose are measured by radio-TLC.

Table 21A. Exemplary Formulations

Formulation	21A-1	21A-2	21A-3	21A-4	21A-5	21A-6	21A-7
²²⁵ Ac-DOTA-TATE	25 µCi/ml	25 µCi/ml	25 µCi/ml	25 µCi/ml	25 µCi/ml	25 µCi/ml	25 µCi/ml
Ascorbic acid	200 mM		200 mM		200 mM		
Sodium ascorbate		100 mM		100 mM		100 mM	100 mM
DTPA	0.05 mg/mL	0.05 mg/mL	1 mg/mL	1 mg/mL	2.5 mg/mL	5 mg/mL	1 mg/mL
Dextran							10%
Aqueous vehicle	saline	saline	saline	saline	saline	saline	saline

Table 21B. Exemplary Formulations

Formulation	21B-1	21B-2	21B-3	21B-4	21B-5	21B-6	21B-7
²²⁵ Ac-DOTA-TOC	25 µCi/ml	25 µCi/ml	25 µCi/ml	25 µCi/ml	25 µCi/ml	25 µCi/ml	15 µCi/ml
Ascorbic acid	200 mM		200 mM		200 mM		
Sodium ascorbate		100 mM		100 mM		100 mM	100 mM
DTPA	0.05 mg/mL	0.05 mg/mL	1 mg/mL	1 mg/mL	2.5 mg/mL	5 mg/mL	1 mg/mL
Dextran							10%
Aqueous vehicle	saline	saline	saline	saline	saline	saline	saline

Table 21C. Exemplary Formulations

Formulation	21C-1	21C-2	21C-3	21C-4	21C-5	21C-6	21C-7
²²⁵ Ac-DOTA-JR-11	25 µCi/ml	25 µCi/ml	25 µCi/ml	25 µCi/ml	25 µCi/ml	25 µCi/ml	32 µCi/ml
Ascorbic acid	200 mM		200 mM		200 mM		
Sodium ascorbate		100 mM		100 mM		100 mM	100 mM
DTPA	0.05 mg/mL	0.05 mg/mL	1 mg/mL	1 mg/mL	2.5 mg/mL	5 mg/mL	1 mg/mL
Dextran							10%
Aqueous vehicle	saline	saline	saline	saline	saline	saline	saline

[362] Example 21. Exemplary Formulations

[363] Formulations of Tables 22A, 22B, and 22C are prepared with similar methods according to Example 9 and Example 19. The mixtures are kept at 20°C-25°C. At different time points, radioactive components of the formulated dose are measured by radio-TLC.

Table 22A. Exemplary Formulations

Formulation	22A-1	22A-2	22A-3	22A-4	22A-5	22A-6	22A-7
²²⁵ Ac-DOTA-TATE	25 µCi/ml	25 µCi/ml	25 µCi/ml	25 µCi/ml	25 µCi/ml	25 µCi/ml	25 µCi/ml
Ascorbic acid	200 mM		200 mM		200 mM		
Sodium ascorbate		100 mM		100 mM		100 mM	100 mM
EDTA	0.05 mg/mL	0.05 mg/mL	1 mg/mL	1 mg/mL	0.1 mg/mL	5 mg/mL	1 mg/mL
Dextran							10%
Aqueous vehicle	saline	saline	saline	saline	saline	saline	saline

Table 22B. Exemplary Formulations

Formulation	22B-1	22B-2	22B-3	22B-4	22B-5	22B-6	22B-7
²²⁵ Ac-DOTA-TOC	25 µCi/ml	25 µCi/ml	25 µCi/ml	25 µCi/ml	25 µCi/ml	25 µCi/ml	15 µCi/ml
Ascorbic acid	200 mM		200 mM		200 mM		
Sodium ascorbate		100 mM		100 mM		100 mM	100 mM
EDTA	0.05 mg/mL	0.05 mg/mL	1 mg/mL	1 mg/mL	0.1 mg/mL	5 mg/mL	1 mg/mL
Dextran							10%
Aqueous vehicle	saline	saline	saline	saline	saline	saline	saline

Table 22C. Exemplary Formulations

Formulation	22C-1	22C-2	22C-3	22C-4	22C-5	21C-6	21C-7
²²⁵ Ac-DOTA-JR-11	25 µCi/ml	25 µCi/ml	25 µCi/ml	25 µCi/ml	25 µCi/ml	25 µCi/ml	32 µCi/ml
Ascorbic acid	200 mM		200 mM		200 mM		
Sodium ascorbate		100 mM		100 mM		100 mM	100 mM
EDTA	0.05 mg/mL	0.05 mg/mL	1 mg/mL	1 mg/mL	0.1 mg/mL	5 mg/mL	1 mg/mL
Dextran							10%
Aqueous vehicle	saline	saline	saline	saline	saline	saline	saline

[364] Example 22. Exemplary Formulations

[365] Formulations of Tables 23A, 23B, and 23C are prepared with similar methods according to Example 9 and Example 19. The mixtures are kept at 20°C-25°C. At different time points, radioactive components of the formulated dose are measured by radio-TLC.

Table 23A. Exemplary Formulations

Formulation	23A-1	23A-2	23A-3	23A-4	23A-5	23A-6	23A-7	23A-8
²²⁵ Ac-DOTA-TATE	25 μCi/ml	25 μCi/ml	25 μCi/ml	25 μCi/ml	25 μCi/ml	25 μCi/ml	32 μCi/ml	32 μCi/ml
Ascorbic acid (mM)	75				75			
Sodium ascorbate (mM)		150				150		
Ethanol (mM)			75				150	
Gentisic acid (mM)				150				100
TETA (mg/mL)	2.5	1						
Macropa (mg/mL)			1	0.1				
PEPA (mg/mL)					0.5	0.5		
TETPA (mg/mL)							0.1	0.1
Aqueous vehicle	saline	saline	saline	saline	saline	saline	saline	saline

Table 23B. Exemplary Formulations

Formulation	23B-1	23B-2	23B-3	23B-4	23A-5	23A-6	23A-7	23A-8
²²⁵ Ac-DOTA-TOC	25 μCi/ml	25 μCi/ml	25 μCi/ml	25 μCi/ml	25 μCi/ml	25 μCi/ml	15 μCi/ml	15 μCi/ml
Ascorbic acid (mM)	75				75			
Sodium ascorbate (mM)		150				150		
Ethanol (mM)			75				150	
Gentisic acid (mM)				150				100
TETA (mg/mL)	2.5	1						
Macropa			1	0.1				

(mg/mL)								
PEPA					0.5	0.5		
(mg/mL)								
TETPA							0.1	0.1
(mg/mL)								
Aqueous vehicle	saline	saline	saline	saline	saline	saline	saline	saline

Table 23C. Exemplary Formulations

Formulation	23C-1	23C-2	23C-3	23C-4	23C-5	23C-6	23C-7	23C-8
²²⁵ Ac-DOTA-JR-11	25 μCi/ml	25 μCi/ml	25 μCi/ml	25 μCi/ml	25 μCi/ml	25 μCi/ml	10 μCi/ml	10 μCi/ml
Ascorbic acid (mM)	75				75			
Sodium ascorbate (mM)		150				150		
Ethanol (mM)			75				150	
Gentisic acid (mM)				150				100
TETA (mg/mL)	2.5	1						
Macropa (mg/mL)			1	0.1				
PEPA (mg/mL)					0.5	0.5		
TETPA (mg/mL)							0.1	0.1
Aqueous vehicle	saline	saline	saline	saline	saline	saline	saline	saline

CLAIMS

We Claim:

1. A liquid radiopharmaceutical composition comprising:
 - (a) a conjugate, wherein the conjugate is ^{225}Ac -DOTA-TATE;
 - (b) one or more stabilizing agents; and
 - (c) an aqueous vehicle.
2. A liquid radiopharmaceutical composition comprising:
 - (a) a conjugate, wherein the conjugate is ^{225}Ac -DOTA-TOC;
 - (b) one or more stabilizing agents; and
 - (c) an aqueous vehicle.
3. A liquid radiopharmaceutical composition comprising:
 - a) a conjugate that comprises
 - (i) a targeting ligand, wherein the targeting ligand binds to a somatostatin receptor (SSR),
 - (ii) a metal chelator covalently attached to the targeting ligand, and
 - (iii) a radionuclide, wherein the radionuclide is ^{225}Ac and is bound to the metal chelator;
 - b) one or more stabilizing agents; and
 - c) an aqueous vehicle.
4. The radiopharmaceutical composition of any one of claims 1-3, wherein the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content bound as part of the conjugate after 72 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC).
5. The radiopharmaceutical composition of any one of claims 1-3, wherein the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content bound as part of the conjugate after 120 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC).
6. The radiopharmaceutical composition of any one of claims 1-4, wherein the radiopharmaceutical composition retains at least 95 % of the ^{225}Ac content bound as part of the conjugate after 120 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC).
7. The radiopharmaceutical composition of any one of claims 1-5, wherein the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content bound as part of the conjugate after 120 hours at about 20°C to about 25°C as determined by high performance liquid chromatography/fraction collection (HPLC-FC).

8. The radiopharmaceutical composition of any one of claims 1-5, wherein the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content bound as part of the conjugate after 72 hours at about 20°C to about 25°C as determined by high performance liquid chromatography/fraction collection (HPLC-FC).
9. The radiopharmaceutical composition of claim 3, wherein the targeting ligand binds to a somatostatin receptor type 1 (SSTR1), somatostatin receptor type 2 (SSTR2), somatostatin receptor type 3 (SSTR3), somatostatin receptor type 4 (SSTR4), and/or somatostatin receptor type 5 (SSTR5).
10. The radiopharmaceutical composition of any one of claims 3 to 9, wherein the targeting ligand is a binding peptide.
11. The radiopharmaceutical composition of claim 10, wherein the binding peptide comprises 6 to 14 amino acid residues.
12. The radiopharmaceutical composition of claim 10 or 11, wherein the binding peptide comprises an amino acid sequence with at least 90% identity to a sequence selected from SEQ IDs 1 to 96.
13. The radiopharmaceutical composition of claim 10 or 11, wherein the binding peptide comprises an amino acid sequence selected from SEQ IDs 1 to 96.
14. The radiopharmaceutical composition of any one of claims 3 to 10, wherein the targeting ligand is octreotate, octreotide, D-Phe¹-cyclo(Cys²-Tyr³-D-Trp⁴-Lys⁵-Thr⁶-Cys⁷)Thr⁸ (tyr³-octreotate or TATE), D-Phe¹-cyclo(Cys²-Tyr³-D-Trp⁴-Lys⁵-Thr⁶-Cys⁷)Thr(ol)⁸ (Phe¹-Tyr³octreotide, edotreotide, or TOC), D-Phe¹-cyclo(Cys²-Phe³-D-Trp⁴-Lys⁵-Thr⁶-Cys⁷)Thr(ol)⁸ (OC), D-Phe¹-cyclo(Cys²-1-Nal-D-Trp⁴-Lys⁵-Thr⁶-Cys⁷)Thr(ol)⁸ (NOC), p-Cl-Phe-cyclo(D-Cys-Aph(Hor)-D-Aph(Cbm)-Lys-Thr-Cys)-D-Tyr-NH₂ (JR-11), or p-Cl-Phe-cyclo(D-Cys-Tyr-D-Aph(Cbm)-Lys-Thr-Cys)-D-Tyr-NH₂ (LM3).
15. The radiopharmaceutical composition of any one of claims 3 to 10, wherein the targeting ligand is JR-11, tyr³-octreotate, edotreotide, octreotate, or octreotide.
16. The radiopharmaceutical composition of any one of claims 3 to 10, wherein the targeting ligand is tyr³-octreotate.
17. The radiopharmaceutical composition of any one of claims 3 to 9, wherein the targeting ligand is a small molecule compound selected from L-797,591, L-779,976, L-796,778, L-803,087, and L-817,818.
18. The radiopharmaceutical composition of any one of claims 3 to 17, wherein a binding affinity of the targeting ligand to a human SSR is not more than 250 nM, as determined by half maximal inhibitory concentration (IC₅₀).
19. The radiopharmaceutical composition of claim 18, wherein the human SSR is SSTR2.

20. The radiopharmaceutical composition of any one of claims 3 to 19, wherein the targeting ligand is covalently linked to the metal chelator through a linker.
21. The radiopharmaceutical composition of any one of claims 3 to 19, wherein the metal chelator is selected from AAZTA, BAT, BAT-TM, Crown, Cyclen, DO2A, CB-DO2A, DO3A, H3HP-DO3A, Oxo-DO3A, p-NH₂-Bn-Oxo-DO3A, DOTA, DOTA-3py, DOTA-PA, DOTA-GA, DOTA-4AMP, DOTA-2py, DOTA-1py, p-SCN-Bn-DOTA, CHX-A''-EDTA, MeO-DOTA-NCS EDTA, DOTAMAP, DOTAGA, DOTAGA-anhydride, DOTMA, DOTASA, DOTAM, DOTP, CB-Cyclam, TE2A, CB-TE2A, CB-TE2P, DM-TE2A, MM-TE2A, NOTA, NOTP, HEHA, HEHA-NCS, p-SCN-Bn-HEHA, DTPA, CHX-A''-DTPA, p-NH₂-Bn-CHX-A''-DTPA, p-SCN-DTPA, p-SCN-Bz-Mx-DTPA, 1B4M-DTPA-DTPA, p-SCN-Bn1B-DTPA, p-SCN-Bn-1B4M-DTPA, p-SCN-Bn-CHX-A''-DTPA, PEPA, p-SCN-Bn-PEPA, TETPA, DOTPA, DOTMP, DOTPM, t-Bu-calix[4]arene-tetracarboxylic acid, macropa, macropa-NCS, macropid, H₃L¹, H₃L⁴, H₂azapa, H₅decapa, bispa², H₄pypa, H₄octapa, H₄CHXoctapa, p-SCN-Bn-H₄octapa, p-SCN-Bn-H₄octapa, TTHA, p-NO₂-Bn-neunpa, H₄octox, H₂macropa, H₂bispa², H₄phospa, H₆phospa, p-SCN-Bn-H₆phospa, TETA, p-NO₂-Bn-TETA, TRAP, TRAP-Pr, TPA, HBED, SHBED, HBED-CC, (HBED-CC)TFP, DMSA, DMPS, DHLA, lipoic acid, TGA, BAL, Bis-thioseminarabazones, p-SCN-NOTA, nNOTA, NODAGA, CB-TE1A1P, 3P-C-NETA-NCS, 3p-C-DEPA, 3P-C-DEPA-NCS, TCMC, PCTA, NODIA-Me, TACN, pycup1A1B, pycup2A, THP, DEDPA, H₂DEDPA, p-SCN-Bn-H₂DEDPA, p-SCN-Bn-TCMC, motexafin, NTA, NOC, 3p-C-NETA, p-NH₂-Bn-TE3A, SarAr, DiAmSar, SarAr-NCS, AmBaSar, BaBaSar, TACN-TM, CP256, C-NE3TA, C-NE3TA-NCS, NODASA, NETA-monoamide, C-NETA, TACN-HSB, NOPO, BPCA, p-SCN-Bn-DRO, DRO-ChX-Mal, DFO, DFO-IAC, DFO-BAC, DiP-LICAM, EC, SBAD, BAPEN, TACHPYR, NEC-SP, L^{Pv}, L1, L2, L3, and EuK-106.
22. The radiopharmaceutical composition of any one of claims 3 to 19, wherein the metal chelator is a metal chelator in FIG. 3 to FIG. 17.
23. The radiopharmaceutical composition of any one of claims 3 to 19, wherein the metal chelator is DOTA.
24. The radiopharmaceutical composition of any one of claims 1 to 23, wherein the one or more stabilizing agents comprise a radiolysis stabilizer.
25. The radiopharmaceutical composition of claim 24, wherein the radiolysis stabilizer is
- a) an amino acid, a peptide or a derivative thereof,
 - b) a vitamin or a derivative thereof,
 - c) a lipid or a derivative thereof,

- d) a carbohydrate or a derivative thereof,
 - e) a volume expander,
 - f) an antioxidant, or
 - g) a combination thereof.
26. The radiopharmaceutical composition of claim 25, wherein the amino acid or peptide is selected from N-Acetyl-L-cysteine, Glutathione, L-Lysine, Selenol-L-methionine, Glutathione, Albumin, Melatonin, Taurine, Alanine, Arginine, Asparagine, Aspartic acid, Cysteine, Glutamine, Glutamic acid, Glycine, Histidine, Isoleucine, Lysine, Methionine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, Valine, and derivatives thereof.
27. The radiopharmaceutical composition of claim 25, wherein the radiolysis stabilizer comprises an antioxidant.
28. The radiopharmaceutical composition of claim 27, wherein the antioxidant is a flavonoid or a derivative thereof.
29. The radiopharmaceutical composition of claim 28, wherein the flavonoid is a catechin or a derivative thereof.
30. The radiopharmaceutical composition of claim 27, wherein the antioxidant is N-acetyl cysteine, Ascorbic acid (e.g., L-ascorbic acid), N-tert-Butyl- α -phenylnitrone, 3-(3,4-Dihydroxyphenyl)-2-propenoic acid (Caffeic Acid), β -Carotene, Provitamin A, (2S,3R)-2-(3,4-Dihydroxyphenyl)-3,4-dihydro-1(2H)-benzopyran-3,5,7-triol 3-(3,4,5-trihydroxybenzoate ((-) Catechin gallate or CG), 1,4,5-Trihydroxycyclohexanecarboxylic acid, trans-4-Hydroxycinnamic acid (p-Coumaric acid), 3,3',4',5',7-Hexahydroxyflavylium chloride, Thiocytic Acid (Dihydrolipoic Acid, DHLA), 4,4',5,5',6,6'-Hexahydroxydiphenic acid 2,6,2',6'-dilactone (Ellagic acid), (-)-cis-3,3',4',5,7-Pentahydroxyflavane (Epi-Catechin or EC), 2-Methoxy-4-(2-propenyl) phenol, trans-4-Hydroxy-3-methoxycinnamic acid (Ferulic acid), 7-Hydroxy-3-(4'-methoxyphenyl)-4H-benzopyran-4-one, all-trans-Fucoanthin, 3,4,5-Trihydroxybenzoic acid (Gallic acid), (2S,3R)-2-(3,4,5-Trihydroxyphenyl)-3,4-dihydro-1(2H)-benzopyran-3,5,7-triol ((-)-Gallocatechin), Glutathione, 2-(3,4-Dihydroxyphenyl)ethanol, 3,4',5,7-Tetrahydroxyflavone (Kaempferol), ($\pm$)-1,2-Dithiolane-3-pentanoic acid, Luteolin, Lycopene, L-Lysine, Neochlorogenic acid, Oleic acid, trans-3,5,4'-Trihydroxystilbene (Resveratrol), 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxychromen-4-one, Rutin hydrate, Selenol-L-methionine, Thiourea, (+)- α -Tocopherol, Xanthophyll, Citric acid (CA), Gentisic acid (GA), Salicylic acid (SA),

Erythorbic acid (EA), Phenol, Sodium bisulfite, Butylated hydroxy anisole, Butylated hydroxy toluene, Metabisulfite, Benzyl alcohol, Thymol, Lipoic acid (LA), Thioglycolic acid (TGA), 2,3 Dimercaptopropan-1-ol (BAL), Zinc, Selenium, Albumin, Ethanol, Mannitol, Sucrose, Melatonin, Ebselen, Pyruvic acid, Carboxy-PTIO, Trolox, Uric acid, Edaravone, Beta carotene, NADPH, Lycopene, Lutein, Catalase, Estrogen, Estradiol, Estriol, Ubiquinol, Copper, Quercetin, Cortisone, Taurine, (2R,3R)-5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-3-yl 3,4,5-trihydroxybenzoate (EpiGallo-Catechin gallate or EGCg), (2R,3R)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3,4-dihydro-2H-chromen-3-yl] 3,4,5-trihydroxybenzoate or Epi-Catechin Gallate (ECG), (2R,3R)-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol (Epigallo-Catechin or EGC), (2R,3S)-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol (Gallo-Catechin or GC), (-)-cis-2-(3,4,5-Trihydroxyphenyl)-3,4-dihydro-1(2H)-benzopyran-3,5,7-triol 3-gallate ((-)-Epigallocatechin-3-O-Gallate), 5-Aminolevulinic Acid hydrate, Ploysorbate 80, Garlic Acid, Sodium L-Ascorbate, Hyaluronic Acid, Dextran 60-90, Selenol, and LysaKare.

31. The radiopharmaceutical composition of claim 25, wherein the radiolysis stabilizer is a vitamin or a derivative thereof.
32. The radiopharmaceutical composition of claim 31, wherein the vitamin or a derivative thereof is selected from L-Ascorbic acid, β -Carotene, Provitamin A, (+)- α -Tocopherol, Erythorbic acid (EA), Trolox, and Lutein, or a salt thereof.
33. The radiopharmaceutical composition of claim 25, wherein the radiolysis stabilizer is a carbohydrate or a derivative thereof.
34. The radiopharmaceutical composition of claim 33, wherein the carbohydrate is Mannitol, Sucrose, Dextran (e.g., Dextran 40, Dextran 70), or Cyclodextrin (e.g., α -cyclodextrin, β -cyclodextrin, and γ -cyclodextrin).
35. The radiopharmaceutical composition of claim 25, wherein the radiolysis stabilizer is a volume expander, and wherein the volume expander is a polymer or a polymer mixture that comprises PEG (e.g., Mn 2000 to 5000), Polygeline, Haemaccel, Gelofusine, PLENVU (polyethylene glycol 3350, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride US FDA 2018 Label), or a combination thereof.
36. The radiopharmaceutical composition of claim 25, wherein the radiolysis stabilizer is selected from N-Acetyl-L-cysteine, L-Ascorbic acid, N-tert-Butyl- α -phenylnitrone, 3-(3,4-Dihydroxyphenyl)-2-propenoic acid (Caffeic Acid), β -Carotene, Provitamin A, (2S,3R)-2-(3,4-Dihydroxyphenyl)-3,4-dihydro-1(2H)-benzopyran-3,5,7-triol 3-(3,4,5-trihydroxybenzoate ((-) Catechin gallate, or CG), 1,4,5-

Trihydroxycyclohexanecarboxylic acid, trans-4-Hydroxycinnamic acid (p-Coumaric acid), 3,3',4',5,5',7-Hexahydroxyflavylium chloride, Thiocytic Acid (Dihydrolipoic Acid, DHLA), 4,4',5,5',6,6'-Hexahydroxydiphenic acid 2,6,2',6'-dilactone (Ellagic acid), (-)-cis-3,3',4',5,7-Pentahydroxyflavane (Epi-Catechin or EC), 2-Methoxy-4-(2-propenyl) phenol, trans-4-Hydroxy-3-methoxycinnamic acid (Ferulic acid), 7-Hydroxy-3-(4'-methoxyphenyl)-4H-benzopyran-4-one, all-trans-Fucoanthin, 3,4,5-Trihydroxybenzoic acid (Gallic acid), (2S,3R)-2-(3,4,5-Trihydroxyphenyl)-3,4-dihydro-1(2H)-benzopyran-3,5,7-triol ((-)-Gallocatechin), Glutathione, 2-(3,4-Dihydroxyphenyl)ethanol, 3,4',5,7-Tetrahydroxyflavone (Kaempferol), ($\pm$)-1,2-Dithiolane-3-pentanoic acid, Luteolin, Lycopene, L-Lysine, Neochlorogenic acid, Oleic acid, trans-3,5,4'-Trihydroxystilbene (Resveratrol), 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxychromen-4-one, Rutin hydrate, Selenol-L-methionine, Thiourea, (+)- α -Tocopherol, Xanthophyll, Alanine and its derivatives, Arginine and its derivatives, Asparagine and its derivatives, Aspartic acid and its derivatives, Cysteine and its derivatives, Glutamine and its derivatives, Glutamic acid and its derivatives, Glycine and its derivatives, Histidine and its derivatives, Isoleucine and its derivatives, Lysine and its derivatives, Methionine and its derivatives, Phenylalanine and its derivatives, Proline and its derivatives, Serine and its derivatives, Threonine and its derivatives, Tryptophan and its derivatives, Tyrosine and its derivatives, Valine and its derivatives, Citric acid (CA), Gentisic acid (GA), Salicylic acid (SA), Erythorbic acid (EA), Phenol, Sodium bisulfite, Butylated hydroxy anisole, Butylated hydroxy toluene, Glutathione, Metabisulfite, Benzyl alcohol, Thymol, Lipoic acid (LA), Thioglycolic acid (TGA), 2,3-Dimercaptopropan-1-ol (BAL), Zinc, Selenium, Albumin, Ethanol, Mannitol, Sucrose, Melatonin, Ebselen, Pyruvic acid, Carboxy-PTIO, Trolox, Uric acid, Edaravone, Beta carotene, NADPH, Lycopene, Lutein, Catalase, Estrogen, Estradiol, Estrinol, Ubiquinol, Copper, Quercetin, Cortisone, 2,3-dimercaptosuccinic acid (DMSA), monisoamyl derivative (MiADMSA), Taurine, Dextran (e.g., Dextran 40, Dextran 70), PEG (e.g., PEG 3350 and PEG 4000), Polygeline, Gelofusine, PLENVU (polyethylene glycol 3350, sodium sulfate, ascorbic acid, sodium chloride and potassium chloride US FDA 2018 Label), Cyclodextrins (e.g., α -cyclodextrin, β -cyclodextrin, and γ -cyclodextrin), (2R,3R)-5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-3-yl 3,4,5-trihydroxybenzoate (EpiGallo-Catechin gallate or EGCg), (2R,3R)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3,4-dihydro-2H-chromen-3-yl] 3,4,5-trihydroxybenzoate or Epi-Catechin Gallate (ECG), (2R,3R)-2-(3,4,5-trihydroxyphenyl)-

- 3,4-dihydro-2H-chromene-3,5,7-triol (Epigallo-Catechin or EGC), (2R,3S)-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol (Gallo-Catechin or GC), or a combination thereof.
37. The radiopharmaceutical composition of claim 25, wherein the radiolysis stabilizer is ascorbic acid or a salt thereof, ethanol, gentisic acid or a salt thereof.
38. The radiopharmaceutical composition of any one of claims 25 to 37, wherein the radiolysis stabilizer is present in the radiopharmaceutical composition at about 0.01 mM to about 5 M.
39. The radiopharmaceutical composition of claim 38, wherein the stabilizing agent is present in the radiopharmaceutical composition from about 5 mM, 10 mM, 25 mM, 50 mM, or 75mM to about 80 mM, 100 mM, 125 mM, 150 mM, 175 mM, 200 mM, 250 mM, or 500 mM.
40. The radiopharmaceutical composition of claim 38, wherein the stabilizing agent is present in the radiopharmaceutical composition at about 10 mM to about 500 mM.
41. The radiopharmaceutical composition of claim 38, wherein the stabilizing agent is present in the radiopharmaceutical composition at about 50 mM to about 200 mM.
42. The radiopharmaceutical composition of any one of claims 25 to 37, wherein the radiolysis stabilizer is present in the radiopharmaceutical composition at about 0.0001 wt% to about 10 wt%.
43. The radiopharmaceutical composition of claim 42, wherein the radiolysis stabilizer is present in the radiopharmaceutical composition at about 0.01 wt% to about 5 wt%, about 0.05 wt% to about 2 wt%, or about 0.1 wt% to about 1 wt%.
44. The radiopharmaceutical composition of any one of claims 25 to 43, wherein the radiolysis stabilizer is present in the radiopharmaceutical composition at a concentration of from about 0.1 to 50 mg/mL.
45. The radiopharmaceutical composition of any one of claims 1 to 44, wherein the one or more stabilizing agents comprise a free metal chelator, wherein the free metal chelator is not attached to the targeting ligand.
46. The radiopharmaceutical composition of claim 45, wherein the free metal chelator is selected from Ethylenediaminetetraacetic acid (EDTA), Diethylenetriaminepentaacetic acid (DTPA), 2-S-(4-Isothiocyanatobenzyl)-1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA), Triethylenetetramine (TETA), 1, 4, 7, 10, 13-pentaazacyclopentadecane-N, N', N'', N''', N''''-pentaacetic acid (PEPA), TETPA, 2,2',2''-(10-(2,6-dioxotetrahydro-2H-pyran-3-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (DOTA-GA), 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic acid (DOTP),

Deferoxamine (DFO), N, N-bis(2-hydroxybenzyl)ethylenediamine-N,N-diacetic acid (HBED), 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic acid) (DOTP), 6,6'-((1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(methylene))dipicolinic acid (Macropa), Meso-2,3-dimercaptosuccinic acid (DMSA), Dimercaptopropane sulfonate (DMPS), Dihydrolipoic acid (DHLA), Lipoic acid (LA), Thioglycolic acid (TGA), 2,3 Dimercaptopropan-1-ol (BAL).

47. The radiopharmaceutical composition of claim 46, wherein the free metal chelator is EDTA, DTPA, or Macropa.
48. The radiopharmaceutical composition of any one of claims 45-47, wherein the free metal chelator is present in the radiopharmaceutical composition at about 0.001 wt% to about 10 wt%.
49. The radiopharmaceutical composition of claim 48, wherein the free metal chelator is present in the radiopharmaceutical composition at about 0.01 wt% to about 5 wt%, about 0.05 wt% to about 2 wt%, or about 0.1 wt% to about 1 wt%.
50. The radiopharmaceutical composition of any one of claims 45-47, wherein the free metal chelator is present in the radiopharmaceutical composition at a concentration of from 0.001 to 50 mg/mL (e.g., 0.01 to 5 mg/mL, 0.01 to 1 mg/mL, 0.01 to 0.5 mg/mL, or 0.01 to 1 mg/mL) .
51. The radiopharmaceutical composition of any one of claims 45-47, wherein the free metal chelator is present in the radiopharmaceutical composition at about 10 mM to about 500 mM.
52. The radiopharmaceutical composition of any one of claims 45-47, wherein the free metal chelator is present in the radiopharmaceutical composition at about 5 mM to 10 mM, 10mM to 25 mM, 25 mM to 50 mM, 50 mM to 75 mM, 75mM to 100 mM, or 100 mM to 200 mM.
53. The radiopharmaceutical composition of any one of claims 1 to 52, wherein the one or more stabilizing agents comprise one or more pH stabilizers.
54. The radiopharmaceutical composition of claim 53, wherein the one or more pH stabilizers comprise an organic acid, or a salt thereof.
55. The radiopharmaceutical composition of claim 54, wherein the organic acid is an acetic acid, fumaric acid, ascorbic acid, propionic acid, benzene sulfonic acid, carbonic acid, citrate acid, aspartic acid, maleic acid, methane sulfonic acid, or tartaric acid.
56. The radiopharmaceutical composition of any one of claims 53-55, wherein the one or more pH stabilizers comprise an inorganic acid, or a salt thereof.

57. The radiopharmaceutical composition of any one of claims 53-56, wherein the one or more pH stabilizers comprise a base, or a salt thereof.
58. The radiopharmaceutical composition of any one of claims 53-57, wherein the one or more pH stabilizers comprise an amino acid or a salt thereof, and wherein the amino acid is glycine, lysine, arginine, histidine or a combination thereof.
59. The radiopharmaceutical composition of any one of claims 53-58, wherein the one or more pH stabilizers comprise an alkaline salt, an acid salt, or both.
60. The radiopharmaceutical composition of claim 59, wherein the alkaline salt is sodium acetate, sodium ascorbate, sodium benzoate, sodium bicarbonate, sodium carbonate, tribasic sodium phosphate acid, dibasic sodium phosphate acid, monobasic sodium phosphate acid, sodium tartrate, sodium lactate, sodium succinate, or disodium succinate.
61. The radiopharmaceutical composition of claim 53, wherein the one or more pH stabilizers comprise Sodium acetate, Sodium ascorbate, Ascorbic acid, Acetic 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, 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, tromethamine (tris), or a combination thereof.
62. The radiopharmaceutical composition of any one of claims 53 to 61, wherein the one or more pH stabilizers are present in the radiopharmaceutical composition at about 0.001 wt% to about 10 wt%.
63. The radiopharmaceutical composition of claim 62, wherein the one or more pH stabilizers are present in the radiopharmaceutical composition at about 0.01 wt% to about 5 wt%, about 0.05 wt% to about 2 wt%, or about 0.1 wt% to about 1 wt%.
64. The radiopharmaceutical composition of any one of claims 53 to 61, wherein the one or more pH stabilizers are present in the radiopharmaceutical composition at a concentration of from 0.1 to 5 mg/mL.
65. The radiopharmaceutical composition of any one of claims 53 to 61, wherein the one or more pH stabilizers are present in the radiopharmaceutical composition at about 10 mM to about 500 mM.
66. The radiopharmaceutical composition of any one of claims 53 to 61, wherein the one or more pH stabilizers are present in the radiopharmaceutical composition at about 0.1 mM

- to 2 mM, 1mM to 2 mM, 1 mM to 10 mM, 5 mM to 10 mM, 5 mM to 15 mM, 1 mM to 15 mM or 1 mM to 25 mM.
67. The radiopharmaceutical composition of any one of claims 53 to 66, wherein the one or more pH stabilizers are configured to maintain a pH of the radiopharmaceutical composition at about 4 to about 8.
68. The radiopharmaceutical composition of any one of claims 53 to 66, wherein the one or more pH stabilizers are configured to maintain a pH of the radiopharmaceutical composition at about 5 to about 7.
69. The radiopharmaceutical composition of any one of claims 1 to 68, wherein the pH of the radiopharmaceutical composition is within a range of about 4 to about 8.
70. The radiopharmaceutical composition of any one of claims 1 to 68, wherein the pH of the radiopharmaceutical composition is about 5.5 to about 6.0.
71. The radiopharmaceutical composition of any one of claims 1 to 70, wherein the composition comprises one or more stabilizing agents selected from Table 2, Table 3, and Table 4.
72. The radiopharmaceutical composition of any one of claims 1 to 71, wherein the aqueous vehicle comprises water, saline solution, dextrose in water, dextrose in saline solution, Ringer's solution, or lactated Ringer's solution.
73. The radiopharmaceutical composition of claim 72, wherein the aqueous vehicle is a saline solution.
74. The radiopharmaceutical composition of any one of claims 1 to 73, wherein the radiopharmaceutical composition is a solution or suspension.
75. The radiopharmaceutical composition of any one of claims 1 to 74, wherein the radiopharmaceutical composition is formulated for IV infusion or bolus injection.
76. The radiopharmaceutical composition of any one of claims 1 to 75, wherein the radiopharmaceutical composition further comprises one or more excipients selected from: a tonicity adjusting agent, a preservative, an antimicrobial agent, a solubilizing agent, a suspending agent, and a surfactant.
77. The radiopharmaceutical composition of any one of claims 20 to 76, wherein the linker comprises one or more groups selected from: substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

78. The radiopharmaceutical composition of any one of claims 1 to 77, wherein the actinium-225 is present in the radiopharmaceutical composition that it provides a volumetric radioactivity of about 5 to 200 kBq/mL.
79. The radiopharmaceutical composition of any one of claims 1 to 78, wherein the actinium-225 is present in the radiopharmaceutical composition that it provides a volumetric radioactivity of about 37 to 11,100 kBq/mL (about 1 to 300 μ Ci/mL), about 185 to 2,220 kBq/mL (about 5 to 60 μ Ci/mL), or about 440 to 851 kBq/mL (about 10 to 30 μ Ci/mL).
80. The radiopharmaceutical composition of any one of claims 1 to 79, wherein the composition retains at least 90 % of the radionuclide content as part of the conjugate after 168 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC).
81. The radiopharmaceutical composition of any one of claims 1 to 79, wherein the composition retains at least 95 % of the radionuclide content as part of the conjugate after 168 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC).
82. The radiopharmaceutical composition of any one of claims 1 to 79, wherein the composition retains at least 85 %, at least 90 %, at least 92 %, at least 95 %, at least 98 % or at least 99 % of the radionuclide content as part of the conjugate after 120 hours at room temperature (about 20°C to about 25°C) as determined by radio thin-layer chromatography (radio-TLC).
83. The radiopharmaceutical composition of any one of claims 1 to 80, wherein the composition retains 95 % or more of the radionuclide content as part of the conjugate after 48 hours, 72 hours, 96 hours, 120 hours, 148 hours, 168 hours, 192 hours, or 216 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC).
84. The radiopharmaceutical composition of any one of claims 1 to 83, wherein the radionuclide is actinium-225, and wherein the composition contains no more than about 5% free actinium-225 after 168 hours at about 20°C to about 25°C, compared to the total amount of the actinium-225 in the composition as determined by radio thin-layer chromatography (radio-TLC).
85. The radiopharmaceutical composition of any one of claims 1 to 84, wherein the radionuclide is actinium-225, and wherein the composition contains no more than about 2% or about 1% free actinium-225 after 168 hours at about 20°C to about 25°C,

compared to the total amount of the actinium-225 in the composition as determined by radio thin-layer chromatography (radio-TLC)

86. The radiopharmaceutical composition of any one of claims 1 to 85, wherein the radionuclide is actinium-225, and wherein the composition contains no more than a total of 5 % of un-chelated daughter isotopes of actinium-225 after 168 hours at about 20°C to about 25°C, compared to the total amount of the actinium-225 in the composition as determined by radio thin-layer chromatography (radio-TLC).
87. The radiopharmaceutical composition of any one of claims 1 to 23, comprising:
- (a) the conjugate, wherein the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 5 to about 100 mCi/L (e.g., about 10 to about 50 mCi/L);
 - (b) a radiolysis stabilizer, wherein the radiolysis stabilizer is present in the radiopharmaceutical composition at a concentration of about 50 to about 500 mM (e.g., about 80 to about 120 mM);
 - (c) optionally a pH stabilizer, optionally a second radiolysis, or both, wherein the second radiolysis stabilizer is optionally present in the radiopharmaceutical composition at concentration of about 1 wt% to about 10wt%;
 - (d) a free metal chelator, wherein the free metal chelator is present in the radiopharmaceutical composition at concentration of about 0.01 mg/mL to about 5 mg/mL (e.g., about 0.01 mg/mL to about 1 mg/mL); and
 - (e) an aqueous vehicle.
88. The radiopharmaceutical composition of claim 87, comprising:
- (a) the conjugate, wherein the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 to 50 mCi/L;
 - (b) a radiolysis stabilizer, wherein the radiolysis stabilizer is ascorbic acid or a salt thereof (e.g., sodium L-ascorbate), ethanol, gentisic acid or a salt thereof, and is present in the radiopharmaceutical composition at a concentration of about 50 mM to about 500 mM (e.g., about 80 to about 120 mM, about 50 mM to about 200 mM);
 - (c) a free metal chelator, wherein the free metal chelator is selected from EDTA, macropa, TETA, PEPA, TETPA, DFO, DOPT, DHLA, TGA, LA, and DTPA, or a combination thereof, and wherein the free metal chelator is present in the radiopharmaceutical composition at a concentration of about 0.01 mg/mL to about 5 mg/mL; and
 - (d) an aqueous vehicle, wherein the aqueous vehicle is saline solution.

89. The radiopharmaceutical composition of any one of claims 1 to 23, comprising:
- (a) the conjugate, wherein the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 to 50 mCi/L;
 - (b) a radiolysis stabilizer;
 - (c) optionally a pH stabilizer, wherein the pH stabilizer is configured to maintain a pH of the radiopharmaceutical composition at about 4 to 8;
 - (d) a free metal chelator, wherein the free metal chelator is configured to maintain a level of free radionuclide in the radiopharmaceutical composition below about 0.05 mCi/L; and
 - (e) an aqueous vehicle.
90. The radiopharmaceutical composition of claim 89, wherein the free metal chelator is configured to maintain a level of free radionuclide in the radiopharmaceutical composition below about 0.05 mCi/L for at least 72 hour at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC).
91. A liquid radiopharmaceutical composition comprising:
- (a) a conjugate that comprises
 - (i) a targeting ligand, wherein the targeting ligand binds to a somatostatin receptor (SSR),
 - (ii) a metal chelator covalently attached to the targeting ligand, and
 - (iii) a radionuclide, wherein the radionuclide is ^{225}Ac ,
 - (b) a means for scavenging free radicals in the radiopharmaceutical composition;
 - (c) a means for scavenging free radionuclide in the radiopharmaceutical composition; and
 - (d) an aqueous vehicle;
- wherein the radiopharmaceutical composition is a solution, and
- wherein the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content as part of the radionuclide after 120 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC).
92. A liquid radiopharmaceutical composition comprising:
- (a) a conjugate that comprises
 - (i) a targeting ligand, wherein the targeting ligand binds to a somatostatin receptor (SSR),
 - (ii) a metal chelator covalently attached to the targeting ligand, and
 - (iii) a radionuclide, wherein the radionuclide is ^{225}Ac ,

- (b) a means for maintaining a pH of the radiopharmaceutical composition, wherein the pH of the radiopharmaceutical composition is about 4 to about 8;
 - (c) a means for scavenging free radionuclide in the radiopharmaceutical composition; and
 - (d) an aqueous vehicle;
- wherein the radiopharmaceutical composition is a solution, and wherein the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content as part of the radionuclide after 120 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC).

93. A liquid radiopharmaceutical composition comprising:

- (a) a conjugate that comprises
 - (i) a targeting ligand, wherein the targeting ligand binds to a somatostatin receptor (SSR),
 - (ii) a metal chelator covalently attached to the targeting ligand, and
 - (iii) a radionuclide, wherein the radionuclide is ^{225}Ac ,wherein the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 1 mCi/L to about 50 mCi/L;
 - (b) a radiolysis stabilizer;
 - (c) a free metal chelator; and
 - (d) an aqueous vehicle;
- wherein the radiopharmaceutical composition is a solution, and wherein the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content as part of the radionuclide after 120 hours at about 20°C to about 25°C as determined by radio thin-layer chromatography (radio-TLC).

94. The liquid radiopharmaceutical composition of any one of claims 91 or 93, wherein the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 mCi/L to about 35 mCi/L.

95. The liquid radiopharmaceutical composition of any one of claims 91 or 93, wherein the conjugate is present in the radiopharmaceutical composition at a concentration equivalent to about 10 mCi/L to about 25 mCi/L.

96. The liquid radiopharmaceutical composition of any one of claims 91 to 95, wherein the conjugate is ^{225}Ac -DOTA-TATE, ^{225}Ac -HA-DOTA-TATE, ^{225}Ac -DOTA-TOC, or ^{225}Ac -DOTA-JR-11.

97. The liquid radiopharmaceutical composition of any one of claims 93 to 96, wherein the radiolysis stabilizer is ascorbic acid, a salt thereof, ethanol, gentisic acid or a salt thereof, or a combination thereof.
98. The liquid radiopharmaceutical composition of any one of claims 93 to 97, wherein the radiolysis stabilizer is present in the radiopharmaceutical composition at a concentration of about 50 mM to about 200 mM.
99. The liquid radiopharmaceutical composition of any one of claims 93 to 98, wherein the free metal chelator is selected from EDTA, macropa, TETA, PEPA, TETPA, DFO, DOPT, DHLA, TGA, LA, and DTPA, or a combination thereof.
100. The liquid radiopharmaceutical composition of any one of claims 93 to 99, wherein the free metal chelator is present in the radiopharmaceutical composition at a concentration of about 0.01mg/mL to about 5 mg/mL.
101. The liquid radiopharmaceutical composition of any one of claims 91 to 100, wherein the composition retains at least 90 % of the ^{225}Ac content as ^{225}Ac -DOTA-TATE after 168 hours at about 20°C to about 25°C.
102. The liquid radiopharmaceutical composition of any one of claims 91 to 100, wherein the conjugate is ^{225}Ac -DOTA-TATE and the radiopharmaceutical composition retains at least 95 % of the ^{225}Ac content as ^{225}Ac -DOTA-TATE after 168 hours at about 20°C to about 25°C.
103. The liquid radiopharmaceutical composition of any one of claims 91 to 102, wherein the conjugate is ^{225}Ac -DOTA-TATE and the radiopharmaceutical composition retains at least 90 % of the ^{225}Ac content bound as part of the conjugate after 120 hours at about 20°C to about 25°C as determined by high performance liquid chromatography/fraction collection (HPLC-FC).
104. The liquid radiopharmaceutical composition of any one of claims 91 to 103, wherein the radiopharmaceutical composition is formulated as a unit dose form that contains about 5 ml to about 50 ml (e.g., about 10-15 ml, about 12mL) of the solution.
105. The liquid radiopharmaceutical composition of any one of claims 91 to 104, wherein the aqueous vehicle is a saline solution.
106. The liquid radiopharmaceutical composition of any one of claims 91 to 105, wherein the radiopharmaceutical composition is formulated for IV infusion.
107. A method of treating a somatostatin receptor-positive (SSTR+) neuroendocrine tumor in a subject in need thereof, comprising administering to the subject an effective amount of a liquid radiopharmaceutical composition of any one of the preceding claim.

108. The method of claim 107, wherein the neuroendocrine tumor is gastroenteropancreatic neuroendocrine tumor (GEP-NET).
109. The method of claim 107 or 108, wherein, prior to the administering of the liquid radiopharmaceutical composition, the subject received ^{177}Lu -DOTA-TATE or ^{177}Lu -DOTA-TOC treatment and the tumor has progressed.
110. The method of any one of claims 107 to 109, wherein the radiopharmaceutical composition is administered to the subject in an amount equivalent to about 60 kBq/kg body weight to 120 kBq/kg body weight per dose.
111. The method of any one of claims 107 to 110, wherein the radiopharmaceutical composition is administered at an 8-week interval.
112. The method of any one of claims 107 to 111, wherein the ^{225}Ac -DOTA-TATE is present in the radiopharmaceutical composition at a concentration equivalent to about 10 mCi/L to about 25 mCi/L.
113. A method of making a radiopharmaceutical composition of any one of claims 1 to 106, comprising:
- a) combining a radionuclide with an un-labeled conjugate, wherein the un-labeled conjugate comprises a targeting ligand and a metal chelator covalently attached to the targeting ligand, thereby producing a labeled conjugate, and
 - b) combining the one or more stabilizing agents with the labeled conjugate.
114. A method of making a radiopharmaceutical composition of any one of claims 1 to 106, comprising:
- a) combining a radionuclide with an un-labeled conjugate in the presence of one or more stabilizer agents, wherein the un-labeled conjugate comprises a targeting ligand and a metal chelator covalently attached to the targeting ligand, thereby producing a mixture comprising a labeled conjugate, and
 - b) optionally combining one or more stabilizing agents to the mixture.
115. A method of treating a disease in a subject in need thereof, comprising administering to the subject the radiopharmaceutical composition of any one of claims 1 to 106.
116. The method of claim 115, wherein the disease is a cancer.
117. The method of claim 116, wherein the cancer is a somatostatin receptor-positive (SSTR+) cancer.
118. The method of any one of claims 107 or 116 to 117, wherein the cancer is a neuroendocrine cancer, a lymphatic cancer, a pancreatic cancer, a pituitary cancer, a breast cancer, a lung cancer, a stomach cancer, medulloblastoma, or neuroblastoma.

119. The method of claim 118, wherein the cancer is a neuroendocrine cancer.
120. The method of claim 107 or 116 to 119, wherein the subject has received a radiotherapy that comprises beta-particle emitting radionuclide prior to the administering of the radiopharmaceutical composition (such as ¹⁷⁷Lu-DOTA-TATE or ¹⁷⁷Lu-DOTA-TOC therapy).
121. The method of any one of claims 119 or 120, wherein the neuroendocrine cancer is a neuroendocrine lung cancer or a neuroendocrine pancreatic cancer.
122. The method of any one of claims 107, 119 or 120, wherein the neuroendocrine cancer is a Carcinoid tumor in the lungs, gastrointestinal tract or thymus, Pancreatic neuroendocrine tumor (e.g., Gastrinoma, Insulinoma, Glucagonoma, VIPoma) Medullary thyroid carcinoma, Merkel cell carcinoma, Pheochromocytoma of the adrenal gland, Adrenal cancer, Small cell carcinoma (such as in the lungs), or Large cell carcinoid tumor (such as in the lungs).
123. The method of any one of claims 116 to 117, wherein the cancer is a SSTR2+ lung neuroendocrine tumor.
124. The method of any one of claims 116 to 117, wherein the cancer is small cell lung cancer (SCLC).
125. The method of any one of claims 116 to 117, wherein the cancer is somatostatin receptor expressing (SSTR+) extensive stage small cell lung cancer (ES-SCLC).
126. The method of claim 124 or 125, wherein the SCLC is untreated, recurrent or refractory.
127. The method of claim 124 or 125, wherein the subject has received at most 1 cycle of platinum- etoposide and PD-L1 inhibitor therapy.
128. The method of any one of claims 116 to 127, wherein the cancer is untreated.
129. The method of any one of claims 116 to 127, wherein the cancer is recurrent or refractory.
130. The method of any one of claims 115 to 129, wherein the radiopharmaceutical composition is administered to the subject in an amount equivalent to about 1kBq/kg to about 0.2GBq/kg body weight per dose.
131. The method of any one of claims 115 to 129, wherein the radiopharmaceutical composition is administered to the subject in an amount equivalent to about 5kBq/kg to about 50,000kBq/kg body weight per dose, about 20k Bq/kg to about 5,000kBq/kg body weight per dose, about 50k Bq/kg to about 500 kBq/kg body weight per dose, or about 50k Bq/kg to about 200 kBq/kg body weight per dose.

132. The method of any one of claims 115 to 131, wherein the radiopharmaceutical composition is administered to the subject in an amount equivalent to about 60 kBq/kg to about 150 kBq/kg body weight per dose.
133. The method of any one of claims 115 to 132, wherein the radiopharmaceutical composition is administered to the subject at a radioactivity of about 1 μ Ci to 1,000 μ Ci, about 10 μ Ci to 500 μ Ci, about 100 μ Ci to 500 μ Ci, about 100 μ Ci to 300 μ Ci, about 125 μ Ci to 275 μ Ci, about 50 μ Ci to 125 μ Ci, or about 10 μ Ci to 50 μ Ci.
134. The method of any one of claims 115 to 132, wherein the radiopharmaceutical composition is administered to the subject at a radioactivity of about 125 μ Ci to 275 μ Ci.
135. The method of any one of claims 115 to 132, wherein the radiopharmaceutical composition is administered to the subject at a radioactivity of about 125 μ Ci, 175 μ Ci, 225 μ Ci, or 275 μ Ci.
136. The method of any one of claims 115 to 135, wherein the radiopharmaceutical composition is administered at an 4 to 6-week interval.
137. A method of treating an SSTR+ cancer in a subject in need thereof, comprising administering to the subject the radiopharmaceutical composition of any one of claims 1 to 106, wherein an H-score of a cancer sample of the subject is at least 11.
138. A method of treating a disease in a subject in need thereof, comprising
- a) determining a level of SSTR expression in a sample of the subject; and
 - b) administering to the subject the radiopharmaceutical composition of any one of claims 1 to 106.
139. The method of claim 138, wherein the level of SSTR expression in a sample is determined by calculating an H-Score, and wherein the H-Score is between 11 and 300.