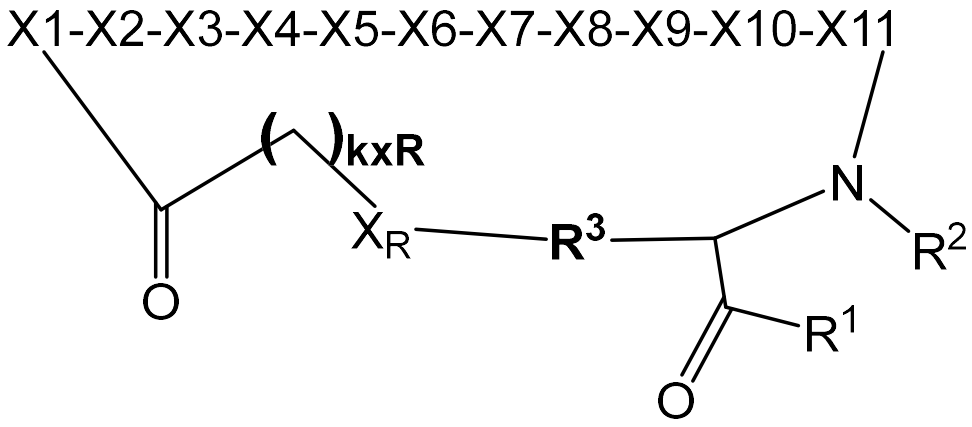
CLAIMS

We claim:

1. A radiopharmaceutical or a pharmaceutically acceptable salt thereof, the radiopharmaceutical comprising:

(a) a peptide of Formula (I-1),



Formula (I-1),

wherein:

R^1 is $-NH_2$ or -OH;

R^2 is C_{1-3} alkyl;

R^3 is C_{1-3} alkylene, optionally substituted with one or more R^4;

each R^4 is independently C_{1-3} alkyl or C_{3-6} cycloalkyl;

kxR is 1, 2, 3, 4, 5, or 6;

X_R is -S-, $-CH_2-$, or -O-;

X1 is any amino acid;

X2 is any amino acid;

X3 is any amino acid;

X4 is any amino acid;

X5 is an amino acid comprising an aromatic ring, or cycloalkyl or heterocycloalkyl group, or X5 is a peptoid;

X6 is a hydrophobic amino acid, a hydrophilic amino acid, or a polar amino acid wherein the polar amino acid has a substituted side chain;

X7 is a hydrophobic amino acid comprising a C_1-C_8 alkyl, cycloalkyl, or heterocycloalkyl, wherein the alkyl, cycloalkyl, and heterocycloalkyl are each independently, optionally substituted;

X8 is A, I, L, V, Y, or F, or a variant thereof;

X9 is an N-alkylated amino acid comprising an aromatic ring;

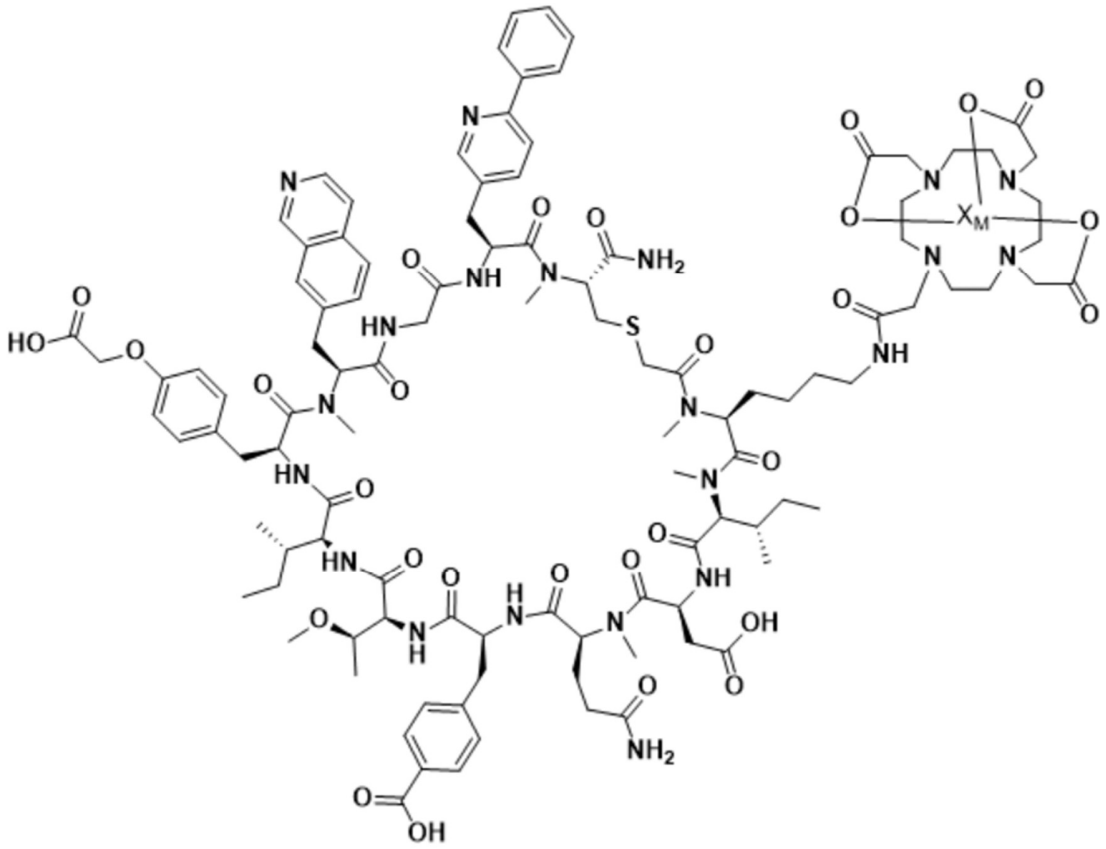
X10 is G or A, or an N-alkylated variant thereof, or a D-amino acid; and

X11 is an amino acid comprising an aromatic ring; and

(b) a metal chelator bound to a radionuclide, wherein the metal chelator is covalently attached to the peptide.

2. The radiopharmaceutical or pharmaceutically acceptable salt thereof of claim 1, wherein the radiopharmaceutical conjugate is selected from Table 3A or Table 3B.

3. The radiopharmaceutical of claim 1, having the following structure:

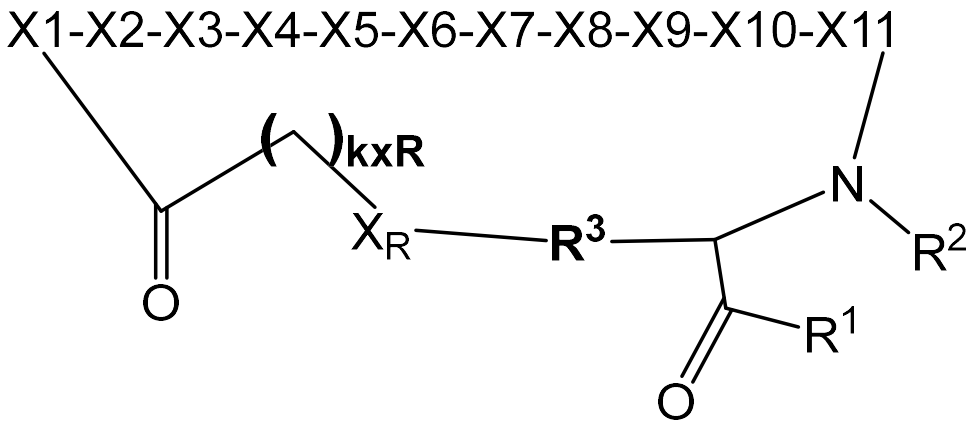


,

or a pharmaceutically acceptable salt thereof, wherein X_M is a radionuclide.

4. A conjugate or a pharmaceutically acceptable salt thereof, the conjugate comprising:

(a) a peptide of Formula (I-1),



Formula (I-1),

wherein:

R^1 is $-NH_2$ or -OH;

R^2 is C_{1-3} alkyl;

R^3 is C_{1-3} alkylene, optionally substituted with one or more R^4;

each R^4 is independently C_{1-3} alkyl or C_{3-6} cycloalkyl;

kxR is 1, 2, 3, 4, 5, or 6;

X_R is -S-, $-CH_2-$, or -O-;

X1 is any amino acid;

X2 is any amino acid;

X3 is any amino acid;

X4 is any amino acid;

X5 is an amino acid comprising an aromatic ring, or cycloalkyl or heterocycloalkyl group, or X5 is a peptoid;

X6 is a hydrophobic amino acid, a hydrophilic amino acid, or a polar amino acid wherein the polar amino acid has a substituted side chain;

X7 is a hydrophobic amino acid comprising a C_1-C_8 alkyl, cycloalkyl, or heterocycloalkyl, wherein the alkyl, cycloalkyl, and heterocycloalkyl are each independently, optionally substituted;

X8 is A, I, L, V, Y, or F, or a variant thereof;

X9 is an N-alkylated amino acid comprising an aromatic ring;

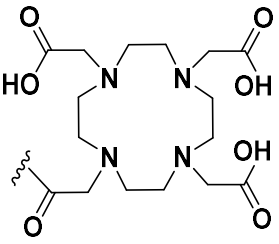
X10 is G or A, or an N-alkylated variant thereof, or a D-amino acid; and

X11 is an amino acid comprising an aromatic ring; and

(b) a metal chelator configured to bind with a radionuclide, wherein the metal chelator is covalently attached to the peptide.

5. The radiopharmaceutical or pharmaceutically acceptable salt thereof of claim 1, or conjugate or pharmaceutically acceptable salt thereof of claim 4, wherein the metal chelator comprises DOTA, DOTA-GA, pBn-DOTA, pBn-SCN-DOTA, NH2-DOTA, NH2-DOTA-GA, p-NCS-Bn-DOTA-GA, p-NH2-Bn-oxo-DO3A, p-SCN-Bn-oxo-DO3A, NOTA, NODA-GA, NH2-NODA-GA, p-NCS-Bn-NODA-GA, p-NH2-Bn-NOTA, p-SCN-Bn-NOTA, NCS-MP-NODA, NH2-MPAA-NODA, PCTA, p-NH2-Bn-PCTA, p-SCN-Bn-PCTA, p-SCN-Bn-HEHA, H2-MACROPA-NCS, H1-MACROPA, H2-MACROPA-NH2, H4-OCTAPA, tetra-(S, S, S, S)-Me-DOTA, tetra-(S, S, S, S)-Et-DOTA, tetra-(S, S, S, S)-iBu-DOTA, or maleimide-nBu-DOTA.

6. The radiopharmaceutical or pharmaceutically acceptable salt thereof, or conjugate or pharmaceutically acceptable salt thereof of claim 5, wherein the metal chelator has the structure:



(DOTA).

7. The radiopharmaceutical or pharmaceutically acceptable salt thereof of any one of claims 1-3 or 5-6, or conjugate or pharmaceutically acceptable salt thereof of any one of claims 4-6, wherein the radionuclide is an alpha particle-emitting radionuclide.

8. The radiopharmaceutical or pharmaceutically acceptable salt thereof, or conjugate or pharmaceutically acceptable salt thereof of claim 7, wherein the alpha particle-emitting radionuclide is Ac-225, Bi-213, Bi-209, Tb-149, Ra-223, Th-227, Fr-223, Gd-148, Th-229, Pb-212, or Po-213.

9. The radiopharmaceutical or pharmaceutically acceptable salt thereof, or conjugate or pharmaceutically acceptable salt thereof of claim 8, wherein the alpha particle-emitting radionuclide is Ac-225.

10. The radiopharmaceutical or pharmaceutically acceptable salt thereof of any one of claims 1-3 or 5-6, or conjugate or pharmaceutically acceptable salt thereof of any one of claims 4-6, wherein the radionuclide is a beta particle-emitting radionuclide.

11. The radiopharmaceutical or pharmaceutically acceptable salt thereof, or conjugate or pharmaceutically acceptable salt thereof of claim 10, wherein the beta particle-emitting radionuclide is Cu-67, Lu-177, Y-90, Rh-105, Yb-175, Tm-167, Pm-153, Sm-153, or In-111.

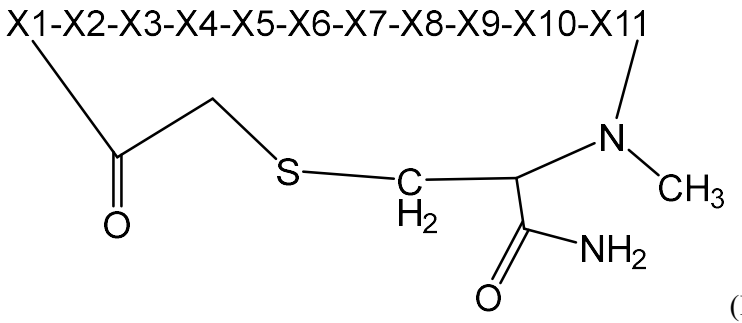
12. The radiopharmaceutical or pharmaceutically acceptable salt thereof, or conjugate or pharmaceutically acceptable salt thereof of claim 11, wherein the beta particle-emitting radionuclide is Lu-177.

13. The radiopharmaceutical or pharmaceutically acceptable salt thereof of any one of claims 1-3 or 5-6, or conjugate or pharmaceutically acceptable salt thereof of any one of claims 4-6, wherein the radionuclide is a positron-emitting radionuclide.

14. The radiopharmaceutical or pharmaceutically acceptable salt thereof, or conjugate or pharmaceutically acceptable salt thereof of claim 13, wherein the positron-emitting radionuclide is Ga-68, Cu-62, Cu-64, Zr-89, or Tb-152.

15. The radiopharmaceutical or pharmaceutically acceptable salt thereof, or conjugate or pharmaceutically acceptable salt thereof of claim 14, wherein the positron-emitting radionuclide is Ga-68.

16. The radiopharmaceutical or pharmaceutically acceptable salt thereof of any one of claims 1 or 5-15, or conjugate or pharmaceutically acceptable salt thereof of any one of claims 4-15, wherein the peptide has the structure of Formula (I-2):



(I-2).

17. The radiopharmaceutical or pharmaceutically acceptable salt thereof of any one of claims 1 or 5-16, or conjugate or pharmaceutically acceptable salt thereof of any one of claims 4-16, wherein:

X1 is I, R, Cit, F4G, 4Py, 3Py, KCOpipzaa, V, Eva, Q, E, MeI, Ahp, F4COO, KCOpip4COO, MeQdMe, MeA, MeSMe, MeG, MeV, MeHseMe, Aib, MeT, allI, TMe, MeKCOpipzaa, MeQ, Hpr, MeTMe, MeDapCOpipzaa, MeE, MeK, MeKAc, MeK(de), MeK(H), MeK(df), or MeK(datb);

X2 is I, K, Cit, F4G, 4Py, 3Py, KCOpipzetOH, V, KCOpipzaa, Eva, Q, E, S, Ahp, F4COO, KCOpip4COO, MeQdMe, MeA, MeSMe, MeG, MeI, MeV, MeL, HseMe, MeY, Me3Py, MeHseMe, MeKAc, allI, TMe, MeTMe, MeK, MeKCOpipzaa, MeQ, Hpr, MeTMe, or MeDapCOpipzaaa;

X3 is D, Har, KCOpipzetOH, Cit, KCOmeglumine, KCOpipzaa, A4paa, Q, A, da, MeA, Abu, Dap, diMeDap, G, MeG, V, E, MeD, S, T, N, Hgl, F4COO, KCOpip4COO, K, KAc, Hgn, MeY, or DapCOpipzaa;

X4 is D, Har, KCOpipzetOH, KCOmeglumine, KCOpipzaa, A4paa, Q, A, E, MeD, S, N, Hgl, F4COO, KCOpip4COO, dd, MeQ, MeQdMe, MeA, MeSMe, MeG, EtG, MeeG, CmG, CmpG, CrmG, CeG, CrpG, MeK, MeKAc, MeHgl, Hgn, MeDapCOpipzaa, MeKCOpipzaa, Medd, Cit, MeCit, MeN, MeS, MeE, MeY, W5N, or MeA4paa;

X5 is Y, F3G, 3Py6COO,4Py2NH2, 3Py5COO, F3COO, 3Py6NHAc, F, F4C, F4OMe, F4COO, MeF4COO, Nal2, F3aao, F4aa, F4aao, 3Py6NHaa, 5Pdo, F3CON, F4F, F4OEt, F4Me, F4CON, F4CONPEG4Me, F3OMe, F3CON, Yae, YaeCOpipzaa, F4aaopipzaa, 4Pdo, 3Py6CON, Atp, Cha4cH, Cha4tH, Cha4cOMe, A1mor, or F4amCOpipzaa;

X6 is I, V, Eva, Chg, Tbg, A, L, Ahp, F4COO, Gcpr, Gcpe, alI, Cle, S3REt, TMe, alTMe, Acpr, Cba, Gthp, NleCOO, NleOH, P, Atb, Nva, Nle, N, DapAc, Abu, Nmm, Ndm, Ncit, Cit, SMe, HseMe, HseEt, HseiPr, dMeS, TdMe, Cbg, NvaOMe, SiPr, Spr, NleOMe, Sbu, Scbm, Scpe, AhpOMe, HseBu, Spent or Hsecpe;

X7 is I, A, L, V, Eva, alI, TMe, SMe, Gcpr, Gcpe, Gthp, dMeS, TdMe, or Cbg;

X8 is A, I, L, V, Y, Cha, Aph, F4OMe, F4COO, F4OEt, F4u, F4Me, F4F, F4CONdMe, F4CON, F4ms, F4CONPEG4Me, F34dOMe, F3OMe, F3C, F3CON, F3CONdMe, 3Py6CON, Yae, YaeCOpipzaa, 5Inda, F3OH, F3aao, F3aa, F4aao, F4aa, 3Py6Nhae, 3Py6NHAc, 3Py6OMe, F4aaopipzaa, or F4amCOpipzaa;

X9 is MeNal2, MeNal27N, MeF34diox, MeF34dOMe, MeF4T, MeY, MeW1Me, MeiW, Me(7Me)6inda, Me(7Me)6indol, Me6inda, MeW7N, MeF3C4Me, or MeF3Me4C;

X10 is G, MeG, A, or a D-amino acid; and

X11 is Bph, 3Py6Ph, F41Me4Pyz, F43Pyz, F44Pyz, F41Pyz, F41Me3Pyz, F41Et4Pyz, F41MeOe4Pyz, F41MeOp4Pyz, F44thp, F4Ac4pip, PhNva, PhNle, Yph, Ybn, F4tb, F4oPr, F4CONdMe, 3Py(6-(2-Py)), 3Py(6-(3-Py)), 3Py(6-(4-Py)), 3Py6(Pip1), 3Py6Imidaz1, 3Py6Me, 3Py6Oxaz5, 3Py6Pipza, 3Py6Pyrazol1, 3Py6Pyrazol3, 3Py6Pyrrol1, Phe(4-(2-Py)), Phe(4-(3-Py)), Phe(4-(4-Py)), or Phe35N4Ph.

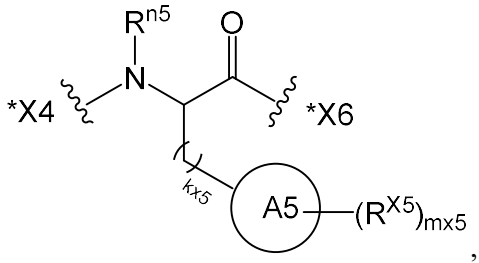
18. The radiopharmaceutical or pharmaceutically acceptable salt thereof of any one of claims 1 or 5-16, or conjugate or pharmaceutically acceptable salt thereof of any one of claims 4-16, wherein:

X1 is any amino acid;

X2 is any amino acid;

X3 is any amino acid;

X4 is any amino acid;

X5 is  , wherein:

R^{n5} is hydrogen or C_{1-3} alkyl;

ring A5 is an aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

each R^{X5} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-SF_5$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^a)R^a$, $-N=S(=O)NR^cR^d$, $-NR^aS(=O)_2R^a$, amidinyl, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-P(=O)(OR^c)(OR^d)$, $-P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, $-L^{X5}$-heterocycloalkyl, $-L^{X5}$-cycloalkyl, $-L^{X5}$-aryl, or $-L^{X5}$-heteroaryl, wherein the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl are optionally substituted with one or more R^{X5a}; or

two R^{X5} are taken together to form =O, =S, or $=N(R^a)$;

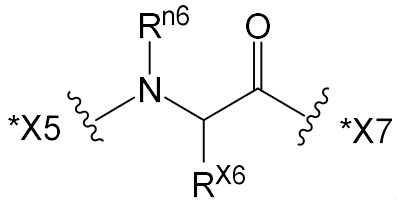
L^{X5} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or $-NR^a-$, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X5a};

kx5 is 0, 1, 2, or 3;

mx5 is 0, 1, 2, 3, 4, or 5;

*X4 represents the point of attachment to X4; and

*X6 represents the point of attachment to X6;

X6 is  , wherein;

R^{n6} is hydrogen or C_{1-3} alkyl;

R^{X6} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, $-L^{X6}$-heterocycloalkyl, $-L^{X6}$-cycloalkyl, $-L^{X6}$-aryl, or $-L^{X6}$-heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl,

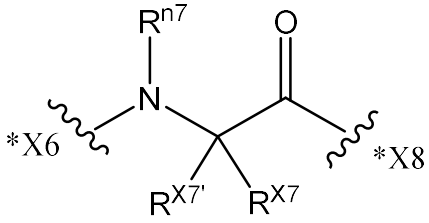
alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X6a}; or

R^{n6} and R^{x6} are taken together with the intervening atoms to form a 5- to 6- membered heterocycloalkyl, which is optionally substituted with one or more R^{X6a};

L^{X6} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X6a};

*X5 represents the point of attachment to X5; and

*X7 represents the point of attachment to X7;

X7 is 

, wherein:

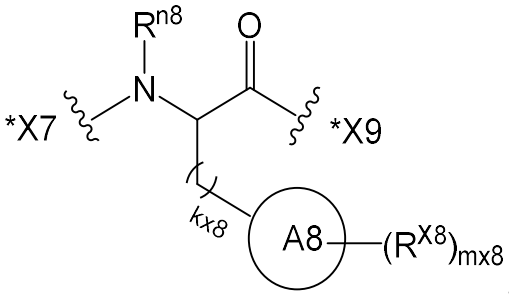
R^{n7} is hydrogen or C_{1-3} alkyl ;

R^{X7} is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cycloalkyl, or heterocycloalkyl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X7a};

$R^{X7'}$ is hydrogen or C_{1-3}alkyl;

*X6 represents the point of attachment to X6; and

*X8 represents the point of attachment to X8;

X8 is 

, wherein;

R^{n8} is hydrogen or C_{1-3}alkyl;

ring A8 is an aryl or heteroaryl;

each R^{X8} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, -CN, -NO_2, -OR^a, -SR^a, -SF_5, -NR^cR^d, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2R^cR^d$, -$S(=O)(=NR^a)R^a$, -$N=S(=O)$ R^cR^d, -$NR^aS(=O)_2R^a$, amidinyl, -$NR^aC(=NH)NR^cR^d$, -$NR^aS(=O)_2R^cR^d$, -$C(=O)R^a$, -$C(=O)OR^a$, -$OC(=O)R^a$, -$OC(=O)OR^a$, -$OC(=O)NR^cR^d$, -$NR^aC(=O)R^a$, -$NR^aC(=O)OR^a$, -$NR^aC(=O)NR^cR^d$, -$C(=O)NR^cR^d$,

-P(=O)(OR^c)(OR^d), -P(=O)R^{c}R^d, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -L^{X8}-heterocycloalkyl, -L^{X8}-cycloalkyl, -L^{X8}-aryl, or -L^{X8}-heteroaryl, wherein each of the alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X8a}; or

two R^{X8} are taken together to form =O, =S, or =N(R^a);

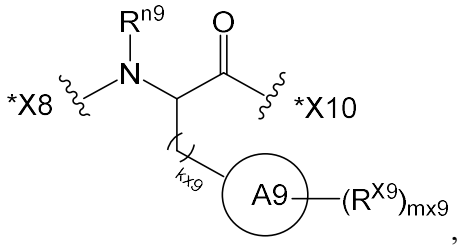
L^{X8} is C$_{1-6}$alkylene, C$_{1-6}$heteroalkylene, -O-, -S-, or -NR^a-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X8a};

kx8 is 0, 1, 2, or 3;

mx8 is 0, 1, 2, 3, 4, or 5;

*X7 represents the point of attachment to X7; and

*X9 represents the point of attachment to X9;

X9 is 

, wherein:

R^{n9} is hydrogen or C$_{1-3}$ alkyl;

ring A9 is an aryl or heteroaryl;

each R^{X9} is independently C$_{1-6}$alkyl, C$_{1-6}$haloalkyl, C$_{1-6}$hydroxyalkyl, C$_{1-6}$aminoalkyl, C$_{1-6}$heteroalkyl, C$_{2-6}$alkenyl, C$_{2-6}$alkynyl, halogen, -CN, -NO$_2$, -OR^a, -SR^a, -SF$_5$, or -NR^{c}R^d, wherein each of the alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^{X9a}; or

two R^{X9} are taken together to form =O, =S, or =N(R^a);

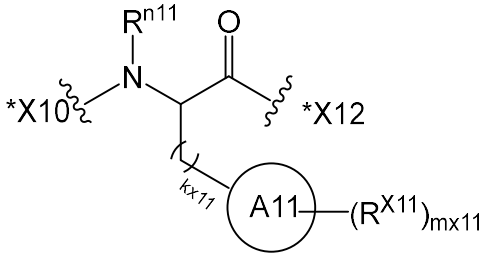
kx9 is 0, 1, 2, or 3;

mx9 is 0, 1, 2, 3, 4, or 5;

*X8 represents the point of attachment to X8; and

*X10 represents the point of attachment to X10;

X10 is glycine, methylglycine, or a D-amino acid;

X11 is , wherein:

R^{n11} is hydrogen or C_{1-3} alkyl;

ring A11 is an aryl or heteroaryl;

each R^{X11} is independently C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6}aminoalkyl, C_{1-6}heteroalkyl, halogen, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-SF_5$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2R^cR^d$, $-S(=O)(=NR^a)R^a$, $-N=S(=O)R^cR^d$, $-NR^aS(=O)_2R^a$, amidinyl, $-NR^aC(=NH)NR^cR^d$, $-NR^aS(=O)_2R^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-P(=O)(OR^c)(OR^d)$, $-P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, $-L^{X11}$-heterocycloalkyl, $-L^{X11}$-cycloalkyl, $-L^{X11}$-aryl, or $-L^{X11}$-heteroaryl, wherein each of the alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl is optionally substituted with one or more R^{X11a}; or

two R^{X11} are taken together to form =O, =S, or $=N(R^a)$;

L^{X11} is C_{1-6}alkylene, C_{1-6}heteroalkylene, -O-, -S-, or $-NR^a$-, wherein the alkylene and heteroalkylene is optionally substituted with one or more R^{X11a};

kx11 is 0, 1, 2, 3, 4, or 5;

mx11 is 0, 1, 2, 3, 4, or 5;

*X10 represents the point of attachment to X10; and

*X12 represents the point of attachment to $N(R^2)$;

each of R^{X5a}, R^{X6a}, R^{X7a}, R^{X8a}, R^{X9a}, and R^{X11a} is independently halogen, C_{1-6} alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NR^cR^d$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-SF_5$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^a)R^a$, $-N=S(=O)R^cR^d$, $-NR^aS(=O)_2R^a$, amidinyl, $-NR^aC(=NH)(NR^a)_2$, $-NR^aS(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^a$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)NR^cR^d$, $-C(=O)NR^cR^d$, $-P(=O)(OR^c)(OR^d)$, $-P(=O)R^cR^d$, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, =O, =S, or $=N(R^a)$, wherein each of the alkyl, heteroalkyl, alkenyl, and alkynyl is optionally substituted with one or more R^e;

each R^a is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or

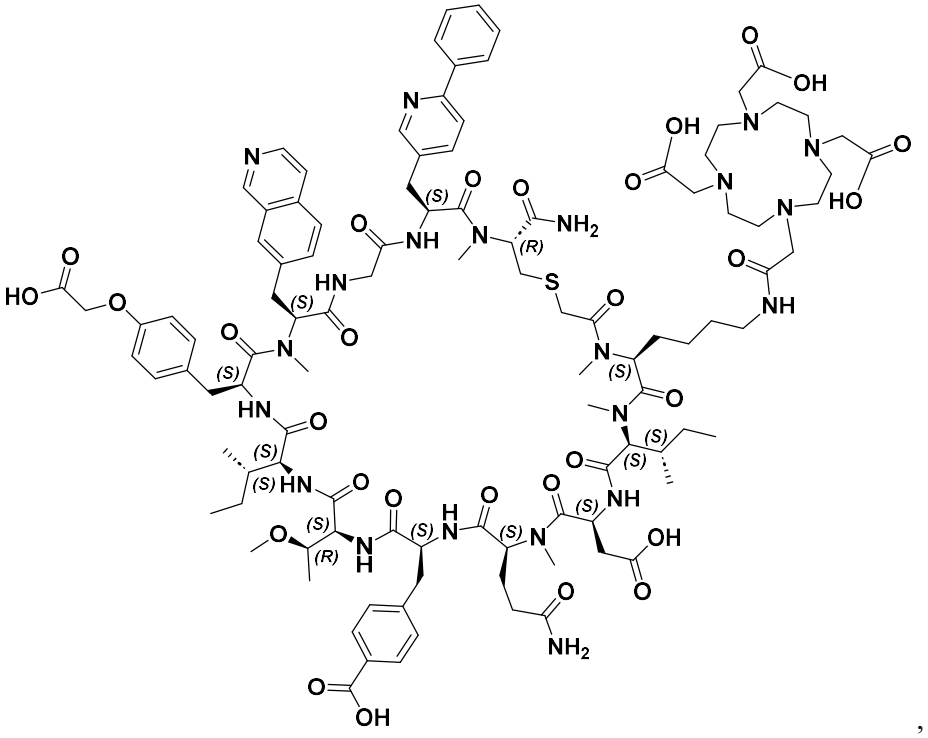
C_1-C_6alkyl(heteroaryl), wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^e;

each R^e is independently halogen, -CN, -OH, -O-C_1-C_6alkyl, -SF_5, -S(=O)C_1-C_6alkyl, -S(=O)$_2$$C_1$-$C_6$alkyl, -S(=O)$_2$$NH_2$, -S(=O)$_2$-halogen, -S(=O)$_2$$NHC_1$-$C_6$alkyl, -S(=O)$_2$$N(C_1$-$C_6$alkyl)$_2$, -$NH_2$, -$NHC_1$-$C_6$alkyl, -$N(C_1$-$C_6$alkyl)$_2$, -NHC(=NH)$NH_2$, -NHC(=O)$OC_1$-$C_6$alkyl, -C(=O)$C_1$-$C_6$alkyl, -C(=O)OH, C_1-C_6alkyl-C(=O)OH, -C(=O)OC_1-C_6alkyl, -C(=O)NH_2, -C(=O)$N(C_1$-C_6alkyl)$_2$, -C(=O)NHC_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl; or two R^e are taken together to form =O; and

each R^c and R^d are independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl), wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R^e; or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R^e.

19. The conjugate or pharmaceutically acceptable salt thereof of claim 5, wherein the conjugate is selected from Table 9.

20. The conjugate of claim 4 having the structure:



,

or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition comprising a radiopharmaceutical or pharmaceutically acceptable salt thereof of any one of claims 1-3 or 5-18, and a pharmaceutically acceptable excipient or carrier.
22. A radiopharmaceutical or pharmaceutically acceptable salt thereof of any one of claims 1-3 or 5-18, or pharmaceutical composition of claim 21 for use in treating a disease or disorder characterized by overexpression of glypican-3 (GPC3) in a subject in need of treatment.
23. Use of a radiopharmaceutical or pharmaceutically acceptable salt thereof of any one of claims 1-3 or 5-18, or pharmaceutical composition of claim 21 in the manufacture of a medicament for treating a disease or disorder characterized by overexpression of glypican-3 (GPC3) in a subject in need of treatment.
24. The radiopharmaceutical or pharmaceutically acceptable salt thereof or pharmaceutical composition for use of claim 22 or the use of claim 23, wherein:

a first radiopharmaceutical or pharmaceutically acceptable salt thereof is to be administered to the subject; and

a therapeutically effective amount of a second radiopharmaceutical or pharmaceutically acceptable salt thereof is to be administered to the subject,

wherein:

the first radiopharmaceutical or pharmaceutically acceptable salt thereof is a radiopharmaceutical or pharmaceutically acceptable salt thereof of any one of claims 1-3, 5-6, and 13-18, wherein the radionuclide is a diagnostic radionuclide; and

the second radiopharmaceutical or pharmaceutically acceptable salt thereof is a radiopharmaceutical or pharmaceutically acceptable salt thereof of any one of claims 1-3, 5-12, and 16-18, wherein the radionuclide is a therapeutic radionuclide.

25. A radiopharmaceutical or pharmaceutically acceptable salt thereof of any one of claims 1-3, 5-6, and 13-18, or pharmaceutical composition of claim 21 for use in diagnosing a disease or disorder characterized by overexpression of GPC3 in a subject in need thereof and imaging the subject, wherein the radionuclide is suitable for use as an imaging isotope.
26. Use of a radiopharmaceutical or pharmaceutically acceptable salt thereof of any one of claims 1-3, 5-6, and 13-18, or pharmaceutical composition of claim 21 in the manufacture of a medicament for diagnosing a disease or disorder characterized by overexpression of GPC3 in a subject in need thereof and imaging the subject, wherein the radionuclide is suitable for use as an imaging isotope.
27. The radiopharmaceutical or pharmaceutically acceptable salt thereof or pharmaceutical composition for use or the use of any one of claims 22-26, wherein the disease or disorder is cancer.
28. The radiopharmaceutical or pharmaceutically acceptable salt thereof or pharmaceutical composition for use or the use of claim 27, wherein the cancer is hepatocellular carcinoma, squamous cell carcinoma of the lung, lung adenocarcinoma, germ cell tumors, hepatoblastoma, wilms tumor, malignant rhabdoid tumors, rhabdomyosarcoma, liposarcoma, thyroid cancers, pancreatic cancer, small bowel cancer, small cell neuroendocrine carcinoma (SCNC), hormonally treated, castration resistant prostatic adenocarcinoma, ovarian cancer, gastric cancer, esophageal carcinoma, or, malignant melanoma.
29. The radiopharmaceutical or pharmaceutically acceptable salt thereof or pharmaceutical composition for use or the use of claim 27 or 28, wherein the cancer is hepatocellular carcinoma (HCC) or hepatoblastoma.
30. A radiopharmaceutical or pharmaceutically acceptable salt thereof of any one of claims 1-3 or 5-18, or pharmaceutical composition of claim 21 for use as a medicament.
31. A kit, tester, or composition for use in diagnosing a disease or disorder characterized by an overexpression or a decreased expression of GPC3, wherein the kit, tester, or composition comprises a radiopharmaceutical, a conjugate, or a pharmaceutically acceptable salt thereof of any one of claims 1-20, or a pharmaceutical composition of claim 21.