IGF-1R MONOCLONAL ANTIBODIES AND USES THEREOF

Related Applications

The present application claims priority to, and the benefit of, U.S. Provisional Patent Application No. 62/502,288, titled "IGF-1R MONOCLONAL ANTIBODIES AND USES THEREOF" and filed on May 5, 2017, and U.S. Provisional Patent Application No. 62/545,945, titled "IGF-1R MONOCLONAL ANTIBODIES AND USES THEREOF" and filed on August 15, 2017. Both of the foregoing applications are hereby incorporated by reference in their entirety for all purposes.

Background

The insulin-like growth factor-1 receptor (IGF-1R) has been evaluated as a potential therapeutic target in the treatment of cancer. The present invention describes an alternate method for leveraging IGF-1R by delivering therapeutic radioisotopes that produce enhanced tumor efficacy with substantially lower doses than that of the antibody alone.

Summary ~~of the Invention~~

The present ~~invention~~disclosure is directed to monoclonal antibodies that target the insulin-like growth factor-1 receptor and the radioimmunoconjugates thereof that demonstrate increased potency and enhance the excretion of a chelating moiety, or a metal complex thereof, when conjugated to a therapeutic moiety, a targeting moiety, or a cross-linking group.

Accordingly, in a first ~~aspect~~example, the ~~invention~~disclosure features a compound having the structure:

$$A\text{-}L^1\text{-}(L^2)_n\text{-}B$$

Formula I

wherein A is chelating moiety or a metal complex thereof;

L^1 is optionally substituted C_1-C_6 alkyl, substituted C_1-C_6 heteroalkyl, substituted aryl or heteroaryl;

B is a therapeutic moiety, a targeting moiety, or cross-linking group,

or a pharmaceutically acceptable salt thereof;

n is 1-5;

each L^2, independently, has the structure:

$$(-X^1\text{-}L^3\text{-}Z^1\text{-})$$

Formula II

wherein is X^1 is $C{=}O(NR^1)$, $C{=}S(NR^1)$, $OC{=}O(NR^1)$, $NR^1C{=}O(O)$, $NR^1C{=}O(NR^1)$, $-CH_2PhC{=}O(NR^1)$, $-CH_2Ph(NH)C{=}S(NR^1)$, O, NR^1 and R^1 is H or optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_6 heteroalkyl, substituted aryl or heteroaryl; L^3 is optionally substituted C_1-C_{50} alkyl or optionally substituted C_1-C_{50} heteroalkyl or C_5-C_{20} polyethylene glycol; Z^1 is CH_2, C=O, C=S, OC=O, $NR^1C{=}O$, NR^1 and R^1 is a hydrogen or optionally substituted C_1-C_6 alkyl, pyrrolidine-2,5-dione.

In one aspect, the present disclosure refers to a compound having a structure of Formula I, or a pharmaceutically acceptable salt thereof:

$A\text{-}L^1\text{-}(L^2)_n\text{-}B$

Formula I

wherein A is a chelating moiety or a metal complex thereof;

L^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted aryl or heteroaryl;

B is an antibody, or antigen binding fragment of the antibody, that specifically binds to IGF-1R, wherein the antibody or antigen binding fragment thereof is selected from the group consisting of figitumumab, cixutumumab, ganitumab, AVE1642, BIIB002, robatumumab, and teprotumumab;

n is 1;

each L^2, independently, has the structure:

$(-X^1\text{-}L^3\text{-}Z^1\text{-})$

Formula II

wherein X^1 is C=O(NR^1) or NR^1, in which R^1 is H or optionally substituted C_1-C_6 alkyl optionally substituted C_1-C_6 heteroalkyl, substituted aryl or heteroaryl;

L^3 is optionally substituted C_1-C_{50} alkyl or optionally substituted C_1-C_{50} heteroalkyl; and

Z^1 is CH_2, C=O, C=S, OC=O, NR^1C=O, or NR^1; in which

R^1 is H, optionally substituted C_1-C_6 alkyl, or pyrrolidine-2,5-dione,

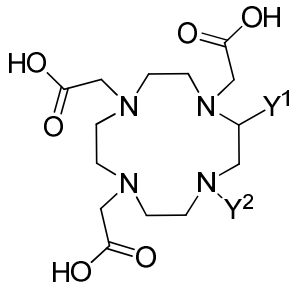
wherein the chelating moiety is DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DOTMA (1R,4R,7R,10R)-α, α', α", α'"-tetramethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, DOTAM (1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane), DOTPA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra propionic acid), DO3AM-acetic acid (2-(4,7,10-tris(2-amino-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid), DOTA-GA anhydride (2,2',2"-(10-(2,6-dioxotetrahydro-2H-pyran-3-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid, DOTP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic acid)), DOTMP (1,4,6,10-tetraazacyclodecane-1,4,7,10-tetramethylene phosphonic acid, DOTA-4AMP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrakis(acetamido-methylenephosphonic acid), CB-TE2A (1,4,8,11-tetraazabicyclo[6.6.2]hexadecane-4,11-diacetic acid), NOTA (1,4,7-triazacyclononane-1,4,7-triacetic acid), NOTP (1,4,7-triazacyclononane-1,4,7-tri(methylene phosphonic acid), TETPA (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetrapropionic acid), TETA (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetra acetic acid), HEHA (1,4,7,10,13,16-hexaazacyclohexadecane-1,4,7,10,13,16-hexaacetic acid), PEPA (1,4,7,10,13-pentaazacyclopentadecane-N,N',N",N"', N""'-pentaacetic acid), H_4octapa (N,N'-bis(6-carboxy-2-pyridylmethyl)-ethylenediamine-N,N'-diacetic acid), H_2dedpa (1,2-[[6-(carboxy)-pyridin-2-yl]-methylamino]ethane), H_6phospa (N,N'-(methylenephosphonate)-N,N'-[6-(methoxycarbonyl)pyridin-2-yl]-methyl-1,2-diaminoethane), TTHA (triethylenetetramine-N,N,N',N",N"', N"'-hexaacetic acid), DO2P (tetraazacyclododecane dimethanephosphonic acid), HP-DO3A (hydroxypropyltetraazacyclododecanetriacetic acid), EDTA (ethylenediaminetetraacetic acid), Deferoxamine, DTPA (diethylenetriaminepentaacetic acid), DTPA-BMA (diethylenetriaminepentaacetic acid-bismethylamide), or porphyrin.

In some ~~embodiment~~examples, the chelating moiety is DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DOTMA (1R,4R,7R,10R)-α, α', α", α'"-tetramethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, DOTAM (1,4,7,10-tetrakis(carbamoylmethyl)-

1,4,7,10-tetraazacyclododecane), DOTPA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra propionic acid), DO3AM-acetic acid (2-(4,7,10-tris(2-amino-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid), DOTA-GA anhydride (2,2',2"-(10-(2,6-dioxotetrahydro-2H-pyran-3-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid, DOTP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic acid)), DOTMP (1,4,6,10-tetraazacyclodecane-1,4,7,10-tetramethylene phosphonic acid, DOTA-4AMP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrakis(acetamido-methylenephosphonic acid), CB-TE2A (1,4,8,11-tetraazabicyclo[6.6.2]hexadecane-4,11-diacetic acid), NOTA (1,4,7-triazacyclononane-1,4,7-triacetic acid), NOTP (1,4,7-triazacyclononane-1,4,7-tri(methylene phosphonic acid), TETPA (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetrapropionic acid), TETA (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetra acetic acid), HEHA (1,4,7,10,13,16-hexaazacyclohexadecane-1,4,7,10,13,16-hexaacetic acid), PEPA (1,4,7,10,13-pentaazacyclopentadecane-N,N',N",N''', N''''-pentaacetic acid), H_4Octapa (N,N'-bis(6-carboxy-2-pyridylmethyl)-ethylenediamine-N,N'-diacetic acid), H_2Dedpa (1,2-[[6-(carboxy)-pyridin-2-yl]-methylamino]ethane), H_6phospa (N,N'-(methylenephosphonate)-N,N'-[6-(methoxycarbonyl)pyridin-2-yl]-methyl-1,2-diaminoethane), TTHA (triethylenetetramine-N,N,N',N",N''', N'''-hexaacetic acid), DO2P (tetraazacyclododecane dimethanephosphonic acid), HP-DO3A (hydroxypropyltetraazacyclododecanetriacetic acid), EDTA (ethylenediaminetetraacetic acid), Deferoxamine, DTPA (diethylenetriaminepentaacetic acid), DTPA-BMA (diethylenetriaminepentaacetic acid-bismethylamide), HOPO (octadentate hydroxypyridinones) or porphyrin.

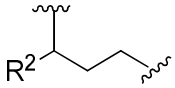
The person having ordinary skill in the art will understand that the use of chelating moieties in the practice of the ~~invention~~disclosure are not limited to the specific constructs disclosed herein, but rather may include other known chelating moieties.

In some ~~embodiment~~examples, the chelating moiety has the structure:



wherein Y^1 is $–CH_2OCH_2(L^2)_n$-B, $C=O(L^2)_n$-B, or $C=S(L^2)_n$-B and Y^2 is $–CH_2CO_2H$;
wherein Y^1 is H, Y^2 is L^1-$(L^2)_n$-B

In some ~~embodiment~~examples, L^1 has the structure:



Formula III

wherein R^2 is optionally substituted hydrogen or $–CO_2H$

In some ~~embodiment~~examples, the metal can be selected from Bi, Pb, Y, Mn, Cr, Fe, Co, Zn, Ni, Tc, In, Ga, Cu, Re, Sm, a lanthanide, or an actinide, for use as imaging or therapeutic agents. Specific examples of radionuclides suitable for complexing to a compound of formula (I) include ^{47}Sc, ^{55}Co,

^{60}Cu, ^{61}Cu, ^{62}Cu, ^{64}Cu, ^{67}Cu, ^{66}Ga, ^{67}Ga, ^{68}Ga, ^{82}Rb, ^{86}Y, ^{87}Y, ^{90}Y, ^{97}Ru, ^{105}Rh, ^{109}Pd, ^{111}In, ^{117m}Sn, ^{149}Pm, ^{149}Tb, ^{153}Sm, ^{177}Lu, ^{186}Re, ^{188}Re, ^{199}Au, ^{201}Tl, ^{203}Pb, ^{212}Pb, ^{212}Bi, ^{213}Bi, ^{225}Ac, and ^{227}Th.

In some ~~embodiment~~examples, B is a therapeutic moiety or targeting moiety.

In some ~~embodiment~~examples, the therapeutic moiety or targeting moiety is an antibody, an antigen-binding fragment thereof or other targeting protein such as nanobodies, affibodies, and consensus sequences from Fibronectin type III domains.

In some ~~embodiment~~examples, the antibody, or an antigen-binding fragment thereof specifically binds insulin-like growth factor-1 receptor (IGF-1R), such as figitumumab, cixutumumab, ganitumab, AVE1642 (also known as humanized EM164 and huEM164), BIIB002, robatumumab, and teprotumumab. In some ~~embodiment~~examples, the antibody, or an antigen binding fragment thereof is AVE1642.

In some ~~embodiment~~examples, the antibody, or antibody-binding fragment thereof includes a light chain variable domain including at least one, two, or all three complementarity determining regions (CDRs) selected from:

(a) CDR-L1 including the amino acid sequence of SEQ ID NO: 1;

(b) CDR-L2 including the amino acid sequence of SEQ ID NO: 2; and

(c) CDR-L3 including the amino acid sequence of SEQ ID NO: 3.

In some ~~embodiment~~examples, the antibody, or antibody-binding fragment thereof includes a heavy chain variable domain including at least one, two, or all three CDRs selected from:

(a) CDR-H1 including the amino acid sequence of SEQ ID NO: 5;

(b) CDR-H2 including the amino acid sequence of SEQ ID NO: 6; and

(c) CDR-H3 including the amino acid sequence of SEQ ID NO: 7.

In certain ~~embodiment~~examples, the antibody, or antibody-binding fragment thereof includes a heavy chain variable domain and a light chain variable domain including at least one, two, three, four, five, or all six CDRs selected from:

(a) CDR-L1 including the amino acid sequence of SEQ ID NO: 1;

(b) CDR-L2 including the amino acid sequence of SEQ ID NO: 2;

(c) CDR-L3 including the amino acid sequence of SEQ ID NO: 3;

(d) CDR-H1 including the amino acid sequence of SEQ ID NO: 5;

(e) CDR-H2 including the amino acid sequence of SEQ ID NO: 6; and

(f) CDR-H3 including the amino acid sequence of SEQ ID NO: 7.

In other ~~embodiment~~examples, the heavy chain variable domain includes the amino acid sequence of SEQ ID NO: 4.

In some ~~embodiment~~examples, the light chain variable domain includes the amino acid sequence of SEQ ID NO: 8.

In some ~~embodiment~~examples, the cross-linking group is an amino-reactive cross-linking group, a methionine-reactive cross-linking group, a thiol-reactive cross-linking group or a sortase-mediated coupling sequence.

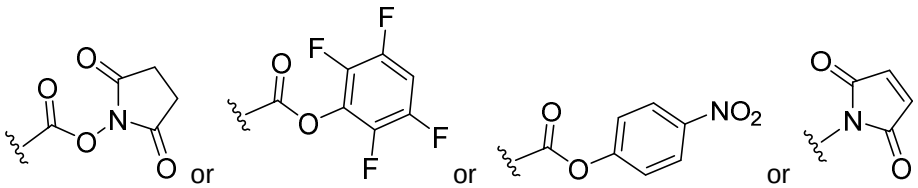
In some ~~embodiment~~examples, the amino-reactive, methionine-reactive, or thiol-reactive cross-linking group comprises an activated ester such as a hydroxysuccinimide ester, N-hydroxysulfosuccinimide, 2,3,5,6-tetrafluorophenol ester, 4-nitrophenol ester or an imidate, anhydride, thiol, disulfide,

maleimide, azide, alkyne, strained alkyne, strained alkene, halogen, sulfonate, haloacetyl, amine, hydrazide, diazirine, phosphine, tetrazine, isothiocyanate, or an oxaziridine.

In some ~~embodiment~~examples, the sortase recognition sequence may comprise of a terminal glycine-glycine-glycine (GGG) and/or LPTXG amino acid sequence, where X is any amino acid.

The person having ordinary skill in the art will understand that the use of cross linking groups in the practice of the ~~invention~~disclosure are not limited to the specific constructs disclosed herein, but rather may include other known cross linking groups.

In some ~~embodiment~~examples, the cross-linking group is selected from the group consisting of:



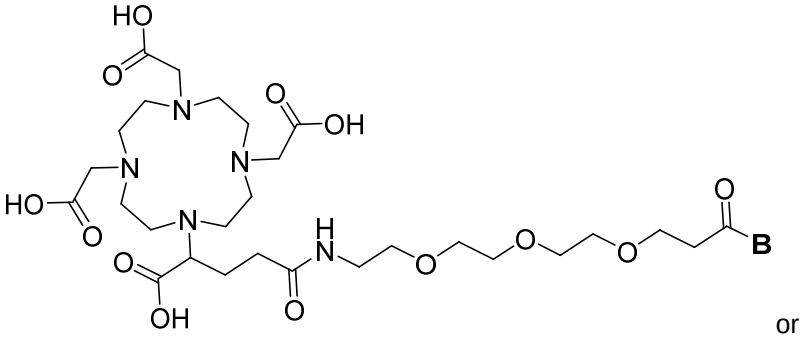
In some ~~embodiment~~examples, Y^1 is H.

In some ~~embodiment~~examples, X^1 is C=O(NR^1) and R^1 is H.

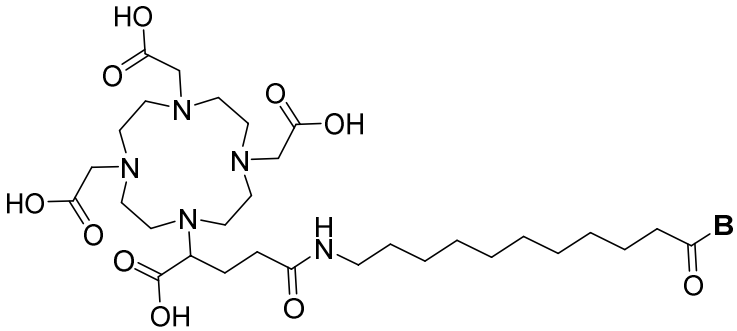
In some ~~embodiment~~examples, Z^1 is $–CH_2$.

In some ~~embodiment~~examples, L^2 has n value of 1.

In some ~~embodiment~~examples, the compound is selected from the group consisting of:



or



In some ~~embodiment~~examples, the metal is a radionuclide.

In some ~~embodiment~~examples, the radionuclide is ^{111}In.

In some ~~embodiment~~examples, the radionuclide is ^{68}Ga.

In some ~~embodiment~~examples, the radionuclide is ^{86}Y.

In some ~~embodiment~~examples, the metal is a beta-emitting radionuclide.

In some ~~embodiment~~examples, the radionuclide are ^{67}Cu, ^{177}Lu, or ^{90}Y

In some ~~embodiment~~examples, the metal is an alpha-emitting radionuclide.

In some ~~embodiment~~examples, the radionuclide is ^{225}Ac, ^{212}Pb, ^{227}Th or the progeny (daughter isotopes) thereof.

In another ~~aspect~~example, the ~~invention~~disclosure features a pharmaceutical composition including any of the foregoing compounds and a pharmaceutically acceptable excipient. In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound as disclosed herein and a pharmaceutically acceptable excipient.

In another ~~aspect~~example, the ~~invention~~disclosure features a method of radiation treatment planning and/or radiation treatment, the method comprising administering to a subject in need thereof any of the foregoing compounds or pharmaceutical compositions. In one aspect, the present disclosure refers to use of a compound as disclosed herein in the manufacture of a medicament for radiation treatment planning and/or radiation treatment, wherein a diagnostically effective amount of the medicament is to be administered to a subject in need thereof and/or a therapeutically effective amount of the medicament is to be administered to a subject in need thereof, wherein the compound in each occurrence comprises a radionuclide.

In another ~~aspect~~example, the ~~invention~~disclosure features a method of detecting and/or treating cancer, the method including administering to a subject in need thereof a first dose of any of the foregoing compounds or pharmaceutical compositions in an amount effective for radiation treatment planning, followed by administering subsequent doses of any of the foregoing compounds or pharmaceutical compositions in a therapeutically effective amount. In one aspect, the present disclosure refers to use of a compound as disclosed herein in the manufacture of a first medicament and use of a compound as disclosed herein in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for treating cancer, wherein a first dose of the first medicament is to be administered in an amount effective for treating cancer to a subject in need thereof, followed by administration of a second dose of the second medicament, wherein the metal of said metal complex is selected from the group consisting of Bi, Pb, Y, Mn, Cr, Fe, Co, Zn, Ni, Tc, In, Ga, Cu, Re, a lanthanide, and an actinide; or the metal of said metal complex is a radionuclide selected from the group consisting of ^{47}Sc, ^{55}Co, ^{60}Cu, ^{61}Cu, ^{62}Cu, ^{64}Cu, ^{67}Cu, ^{66}Ga, ^{67}Ga, ^{68}Ga, ^{82}Rb, ^{86}Y, ^{87}Y, ^{90}Y, ^{97}Ru, ^{99m}Tc, ^{105}Rh, ^{109}Pd, ^{111}In, ^{117m}Sn, ^{149}Pm, ^{149}Tb ^{153}Sm, ^{177}Lu, ^{186}Re, ^{188}Re, ^{199}Au, ^{201}Tl, ^{203}Pb, ^{212}Pb, ^{212}Bi, ^{213}Bi, ^{225}Ac, and ^{227Th}.

In some ~~embodiment~~examples, the compound or composition administered in the first dose and the compound or composition administered in the second dose, or subsequent doses are the same.

In some ~~embodiment~~examples, the compound or composition administered in the first dose and the compound or composition administered in the second dose, or subsequent doses are different.

In some ~~embodiment~~examples, the cancer is a solid tumor or hematologic (liquid) cancer.

In some ~~embodiment~~examples, the solid tumor cancer is breast cancer, non-small cell lung cancer, small cell lung cancer, pancreatic cancer, head and neck cancer, prostate cancer, colorectal cancer, sarcoma, adrenocortical carcinoma, neuroendocrine cancer, Ewing's Sarcoma, multiple myeloma, or acute myeloid leukemia.

In some ~~embodiment~~examples, the foregoing methods further include administering an antiproliferative agent, radiation sensitizer, or an immunoregulatory or immunomodulatory agent.

In some ~~embodiment~~examples, any of the foregoing compounds or compositions thereof and an antiproliferative agent or radiation sensitizer are administered within 28 days (e.g., within 14, 7, 6, 5, 4, 3, 2, or 1 day(s)) of each other.

In some ~~embodiment~~examples, any of the above-described compounds or compositions thereof and an immunoregulatory or immunomodulatory agent are administered within 90 days (e.g., within 80, 70, 60, 50, 40, 30, 20, 10, 5, 4, 3, 2, or 1 day(s)) of each other.

In another ~~aspect~~example, the ~~invention~~disclosure features a method of making a radioconjugate (e.g., any of the radioconjugates described herein). The method includes the steps of (a) conjugating a bifunctional chelate to a biological molecule, (b) purifying the conjugate produced by step (a), and (c) chelating one or more radionuclides (e.g., one or more Ac-225 radionuclides) with the purified conjugate of step (b) at a temperature of less than 35°C (e.g., 20-25°C) to produce a radioconjugate (e.g. an actinium radioconjugate).

In some ~~embodiment~~examples, the radioconjugate is a radioimmunoconjugate (e.g., any of the radioimmunoconjugates described herein).

In some ~~embodiment~~examples, the pH of the reaction mixture of conjugation step (a) is less than 6.4 (e.g., 6.3, 6.2, 6.1, 6.0, 5.9, or 5.8 or less).

In some ~~embodiment~~examples, the pH of the reaction mixture of conjugation step (c) is less than 5.5 (e.g., 5.4, 5.3, 5.2, 5.1, or 5.0 or less) or more than 7.0 (e.g., 7.1, 7.2, 7.3, 7.4, 7.5 or more).

In some ~~embodiment~~examples, the temperature of the reaction mixture of conjugation step (c) is 20-34°C (e.g., 21°C, 22°C, 23°C, 24°C, 25°C, 26°C, 27°C, 28°C, 29°C, 30°C, 31°C, 32°C, 33°C, or 34°C).

Chemical Terms:

The term "acyl," as used herein, represents a hydrogen or an alkyl group (e.g., a haloalkyl group), as defined herein, that is attached to the parent molecular group through a carbonyl group, as defined herein, and is exemplified by formyl (i.e., a carboxyaldehyde group), acetyl, trifluoroacetyl, propionyl, butanoyl and the like. Exemplary unsubstituted acyl groups include from 1 to 7, from 1 to 11, or from 1 to 21 carbons. In some embodiments, the alkyl group is further substituted with 1, 2, 3, or 4 substituents as described herein.

The term "alkyl," as used herein, is inclusive of both straight chain and branched chain saturated groups from 1 to 20 carbons (e.g., from 1 to 10 or from 1 to 6), unless otherwise specified. Alkyl groups are exemplified by methyl, ethyl, n- and iso-propyl, n-, sec-, iso- and tert-butyl, neopentyl, and the like, and may be optionally substituted with one, two, three, or, in the case of alkyl groups of two carbons or more, four substituents independently selected from the group consisting of: (1) C_{1-6} alkoxy; (2) C_{1-6} alkylsulfinyl; (3) amino, as defined herein (e.g., unsubstituted amino (i.e., $-NH_2$) or a substituted amino (i.e., $-N(R^{N1})_2$, where R^{N1} is as defined for amino); (4) C_{6-10} aryl-C_{1-6} alkoxy; (5) azido; (6) halo; (7) (C_{2-9} heterocyclyl)oxy; (8) hydroxy, optionally substituted with an *O*-protecting group; (9) nitro; (10) oxo (e.g., carboxyaldehyde or acyl); (11) C_{1-7} spirocyclyl; (12) thioalkoxy; (13) thiol; (14) $-CO_2R^{A'}$, optionally substituted with an *O*-protecting group and where $R^{A'}$ is selected from the group consisting of (a) C_{1-20} alkyl (e.g., C_{1-6} alkyl), (b) C_{2-20} alkenyl (e.g., C_{2-6} alkenyl), (c) C_{6-10} aryl, (d) hydrogen, (e) C_{1-6} alk-C_{6-10} aryl, (f) amino-C_{1-20} alkyl, (g) polyethylene glycol of $-(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl, and (h) amino-polyethylene glycol of $-NR^{N1}(CH_2)_{s2}(CH_2CH_2O)_{s1}(CH_2)_{s3}NR^{N1}$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C_{1-6} alkyl; (15) $-C(O)NR^{B'}R^{C'}$, where each of $R^{B'}$ and $R^{C'}$ is, independently, selected from the group consisting of (a) hydrogen, (b) C_{1-6} alkyl, (c) C_{6-10} aryl, and (d) C_{1-6} alk-C_{6-10} aryl; (16) $-SO_2R^{D'}$, where $R^{D'}$ is selected from the group consisting of (a) C_{1-6} alkyl, (b) C_{6-10} aryl, (c) C_{1-6} alk-C_{6-10} aryl, and (d) hydroxy; (17) $-SO_2NR^{E'}R^{F'}$, where each of $R^{E'}$ and $R^{F'}$ is, independently, selected from the group consisting of (a) hydrogen, (b) C_{1-6} alkyl, (c) C_{6-10} aryl and (d) C_{1-6} alk-C_{6-10} aryl; (18) $-C(O)R^{G'}$, where $R^{G'}$ is selected from the group consisting of (a) C_{1-20} alkyl (e.g., C_{1-6} alkyl), (b) C_{2-20} alkenyl (e.g., C_{2-6} alkenyl), (c) C_{6-10} aryl, (d) hydrogen, (e) C_{1-6} alk-C_{6-10} aryl, (f) amino-C_{1-20} alkyl, (g) polyethylene glycol of $-(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl, and (h) amino-

CLAIMS

1. A compound having ~~a~~the structure of Formula I, or a pharmaceutically acceptable salt thereof:

$A\text{-}L^1\text{-}(L^2)_n\text{-}B$

Formula I

wherein A is a chelating moiety or a metal complex thereof;

L^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted aryl or heteroaryl;

B is an antibody, or antigen binding fragment ~~thereof~~of the antibody, that specifically binds to IGF-1R, wherein the antibody or antigen binding fragment thereof is selected from the group consisting of figitumumab, cixutumumab, ganitumab, AVE1642, BIIB002, robatumumab, and teprotumumab;

~~or a pharmaceutically acceptable salt thereof;~~

n is 1~~-5~~;

each L^2, independently, has the structure:

$(\text{-}X^1\text{-}L^3\text{-}Z^1\text{-})$

Formula II

wherein ~~is~~ X^1 is $C{=}O(NR^1)$~~, C=S(NR¹), OC=O(NR¹), NR¹C=O(O), NR¹C=O(NR¹), -CH₂PhC=O(NR¹), -CH₂Ph(NH)C=S(NR¹) , O,~~ or NR^1, ~~and~~ in which R^1 is H or optionally substituted C_1-C_6 alkyl ~~or~~ optionally substituted C_1-C_6 heteroalkyl, substituted aryl or heteroaryl;

L^3 is optionally substituted C_1-C_{50} alkyl or optionally substituted C_1-C_{50} heteroalkyl ~~or C_5-C_{20} polyethylene glycol~~; and

Z^1 is CH_2, C=O, C=S, OC=O, $NR^1C{=}O$, or NR^1; in which~~and~~

R^1 is H~~a hydrogen or,~~ optionally substituted C_1-C_6 alkyl, or pyrrolidine-2,5-dione,

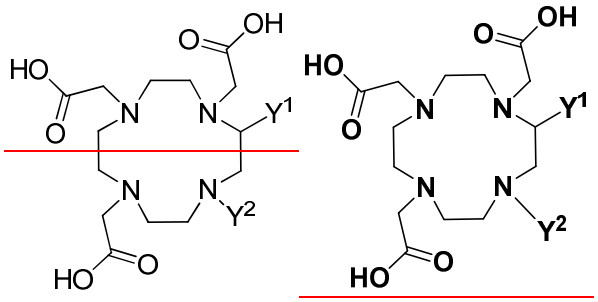
wherein the chelating moiety is DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DOTMA (1R,4R,7R,10R)-α, α', α", α'"-tetramethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, DOTAM (1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane), DOTPA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra propionic acid), DO3AM-acetic acid (2-(4,7,10-tris(2-amino-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid), DOTA-GA anhydride (2,2',2"-(10-(2,6-dioxotetrahydro-2H-pyran-3-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid, DOTP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic acid)), DOTMP (1,4,6,10-tetraazacyclodecane-1,4,7,10-tetramethylene phosphonic acid, DOTA-4AMP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrakis(acetamido-methylenephosphonic acid), CB-TE2A (1,4,8,11-tetraazabicyclo[6.6.2]hexadecane-4,11-diacetic acid), NOTA (1,4,7-triazacyclononane-1,4,7-triacetic acid), NOTP (1,4,7-triazacyclononane-1,4,7-tri(methylene phosphonic acid), TETPA (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetrapropionic acid), TETA (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetra acetic acid), HEHA (1,4,7,10,13,16-hexaazacyclohexadecane-1,4,7,10,13,16-hexaacetic acid), PEPA (1,4,7,10,13-pentaazacyclopentadecane-N,N',N",N"', N""-pentaacetic acid), H_4octapa (N,N'-bis(6-carboxy-

2-pyridylmethyl)-ethylenediamine-N,N'-diacetic acid), H_2dedpa (1,2-[[6-(carboxy)-pyridin-2-yl]-methylamino]ethane), H_6phospa (N,N'-(methylenephosphonate)-N,N'-[6-(methoxycarbonyl)pyridin-2-yl]-methyl-1,2-diaminoethane), TTHA (triethylenetetramine-N,N,N',N",N''', N'''-hexaacetic acid), DO2P (tetraazacyclododecane dimethanephosphonic acid), HP-DO3A (hydroxypropyltetraazacyclododecanetriacetic acid), EDTA (ethylenediaminetetraacetic acid), Deferoxamine, DTPA (diethylenetriaminepentaacetic acid), DTPA-BMA (diethylenetriaminepentaacetic acid-bismethylamide), or porphyrin.

~~2. The compound in claim 1, wherein said the chelating moiety is DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DOTMA (1R,4R,7R,10R)-α, α', α", α'"-tetramethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, DOTAM (1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane), DOTPA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra propionic acid), DO3AM-acetic acid (2-(4,7,10-tris(2-amino-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid), DOTA-GA anhydride (2,2',2"-(10-(2,6-dioxotetrahydro-2H-pyran-3-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid, DOTP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic acid)), DOTMP (1,4,6,10-tetraazacyclodecane-1,4,7,10-tetramethylene phosphonic acid, DOTA-4AMP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrakis(acetamido-methylenephosphonic acid), CB-TE2A (1,4,8,11-tetraazabicyclo[6.6.2]hexadecane-4,11-diacetic acid), NOTA (1,4,7-triazacyclononane-1,4,7-triacetic acid), NOTP (1,4,7-triazacyclononane-1,4,7-tri(methylene phosphonic acid), TETPA (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetrapropionic acid), TETA (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetra acetic acid), HEHA (1,4,7,10,13,16-hexaazacyclohexadecane-1,4,7,10,13,16-hexaacetic acid), PEPA (1,4,7,10,13-pentaazacyclopentadecane-N,N',N",N''', N''''-pentaacetic acid), H_4octapa (N,N'-bis(6-carboxy-2-pyridylmethyl)-ethylenediamine-N,N'-diacetic acid), H_2dedpa (1,2-[[6-(carboxy)-pyridin-2-yl]-methylamino]ethane), H_6phospa (N,N'-(methylenephosphonate)-N,N'-[6-(methoxycarbonyl)pyridin-2-yl]-methyl-1,2-diaminoethane), TTHA (triethylenetetramine-N,N,N',N",N''', N'''-hexaacetic acid), DO2P (tetraazacyclododecane dimethanephosphonic acid), HP-DO3A (hydroxypropyltetraazacyclododecanetriacetic acid), EDTA (ethylenediaminetetraacetic acid), Deferoxamine, DTPA (diethylenetriaminepentaacetic acid), DTPA-BMA (diethylenetriaminepentaacetic acid-bismethylamide), or porphyrin.~~

2. The compound of claim 1, wherein the chelating moiety is selected from the group consisting of DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DOTMA (1R,4R,7R,10R)-α, α', α", α'"-tetramethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, DOTAM (1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane), DOTPA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra propionic acid), DO3AM-acetic acid (2-(4,7,10-tris(2-amino-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid), DOTA-GA anhydride (2,2',2"-(10-(2,6-dioxotetrahydro-2H-pyran-3-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid, DOTP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic acid)), and DOTA-4AMP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrakis(acetamido-methylenephosphonic acid).

3. The compound of claim 2, wherein the ~~chelating moiety has the~~ structure of Formula I is:



~~W~~wherein Y^1 is $–CH_2OCH_2(L^2)_n$-B, $C=O(L^2)_n$-B, or $C=S(L^2)_n$-B and Y^2 is $–CH_2CO_2H$; or

~~W~~wherein Y^1 is H~~,~~ and Y^2 is L^1-$(L^2)_n$-B,

L^2, independently,

$(-X^1\text{-}L^3\text{-}Z^1-)$

Formula II

wherein X^1 is $C=O(NR^1)$ or NR^1, R^1 is H or optionally substituted C_1-C_6 alkyl optionally substituted C_1-C_6 heteroalkyl, substituted aryl or heteroaryl; L^3 is optionally substituted C_1-C_{50} alkyl or optionally substituted C_1-C_{50} heteroalkyl; and Z^1 is CH_2, C=O, C=S, OC=O, $NR^1C=O$, or NR^1; R^1 is H, optionally substituted C_1-C_6 alkyl, or pyrrolidine-2,5-dione,

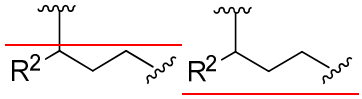
wherein the chelating moiety is DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DOTMA (1R,4R,7R,10R)-α, α', α", α'"-tetramethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, DOTAM (1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane), DOTPA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra propionic acid), DO3AM-acetic acid (2-(4,7,10-tris(2-amino-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid), DOTA-GA anhydride (2,2',2"-(10-(2,6-dioxotetrahydro-2H-pyran-3-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid, DOTP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic acid)), DOTMP (1,4,6,10-tetraazacyclodecane-1,4,7,10-tetramethylene phosphonic acid, DOTA-4AMP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrakis(acetamido-methylenephosphonic acid), CB-TE2A (1,4,8,11-tetraazabicyclo[6.6.2]hexadecane-4,11-diacetic acid), NOTA (1,4,7-triazacyclononane-1,4,7-triacetic acid), NOTP (1,4,7-triazacyclononane-1,4,7-tri(methylene phosphonic acid), TETPA (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetrapropionic acid), TETA (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetra acetic acid), HEHA (1,4,7,10,13,16-hexaazacyclohexadecane-1,4,7,10,13,16-hexaacetic acid), PEPA (1,4,7,10,13-pentaazacyclopentadecane-N,N',N",N"', N""-pentaacetic acid), H_4octapa (N,N'-bis(6-carboxy-2-pyridylmethyl)-ethylenediamine-N,N'-diacetic acid), H_2dedpa (1,2-[[6-(carboxy)-pyridin-2-yl]-methylamino]ethane), H_6phospa (N,N'-(methylenephosphonate)-N,N'-[6-(methoxycarbonyl)pyridin-2-yl]-methyl-1,2-diaminoethane), TTHA (triethylenetetramine-N,N,N',N",N"', N"'-hexaacetic acid), DO2P (tetraazacyclododecane dimethanephosphonic acid), HP-DO3A (hydroxypropyltetraazacyclododecanetriacetic acid), EDTA (ethylenediaminetetraacetic acid), Deferoxamine, DTPA (diethylenetriaminepentaacetic acid), DTPA-BMA (diethylenetriaminepentaacetic acid-bismethylamide), or porphyrin;

n is 1;

B is an antibody, or antigen binding fragment of the antibody, that specifically binds to IGF-1R, wherein the antibody or antigen binding fragment thereof is selected from the group consisting of figitumumab, cixutumumab, ganitumab, AVE1642, BIIB002, robatumumab, and teprotumumab; and

L^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted aryl or heteroaryl.

4. The compound of claim 1~~any one of claims 1 to 3~~, wherein L^1 is~~has the structure~~:



Formula III

~~W~~wherein R^2 is ~~optionally substituted~~ hydrogen or $–CO_2H$.

5. The compound~~s~~ of claim 1~~in claim 1-4~~, wherein the~~said~~ metal of said metal complex is ~~can be~~ selected from the group consisting of Bi, Pb, Y, Mn, Cr, Fe,

Co, Zn, Ni, Tc, In, Ga, Cu, Re, ~~Sm,~~ a lanthanide, and~~or~~ an actinide; or~~, for use as imaging or therapeutic agents.~~

the metal of said metal complex is a~~Specific examples of~~ radionuclide~~s~~ selected from the group consisting of~~suitable for complexing to a compound of formula (I) include~~ ^{47}Sc, ^{55}Co, ^{60}Cu, ^{61}Cu, ^{62}Cu, ^{64}Cu, ^{67}Cu, ^{66}Ga, ^{67}Ga, ^{68}Ga, ^{82}Rb, ^{86}Y, ^{87}Y, ^{90}Y, ^{97}Ru, ^{99m}Tc, ^{105}Rh, ^{109}Pd, ^{111}In, ^{117m}Sn, ^{149}Pm, ^{149}Tb ^{153}Sm, ^{177}Lu, ^{186}Re, ^{188}Re, ^{199}Au, ^{201}Tl, ^{203}Pb, ^{212}Pb, ^{212}Bi, ^{213}Bi, ^{225}Ac, and ^{227}Th.

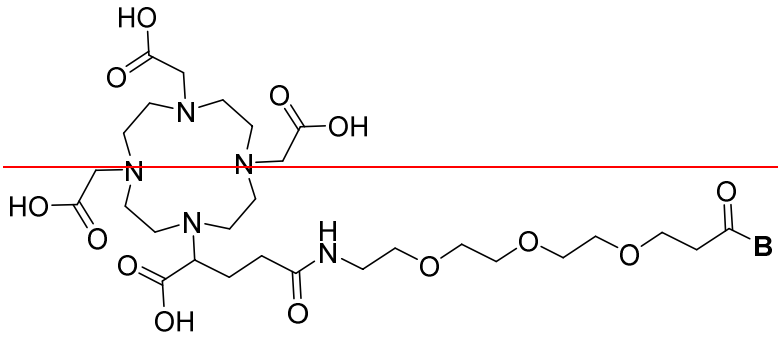
6. The compound of claim 3~~any one of claims 3 to 5~~, wherein Y^1 is H.

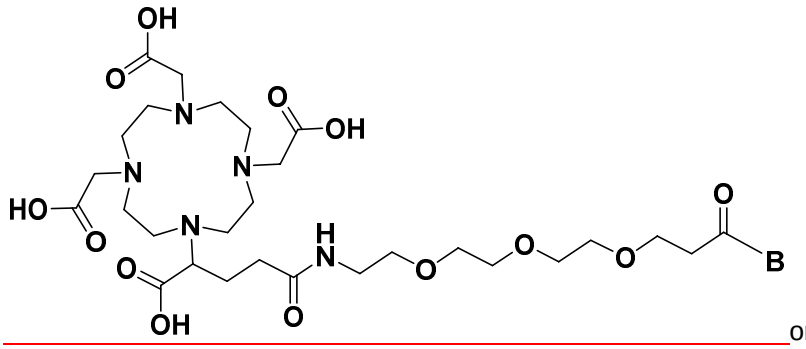
7. The compound of claim 1,~~any one of claims 1-6~~ wherein X^1 is C=O(NR^1) and R^1 is H.

8. The compound of claim 1~~any one of claims 1-7~~, wherein Z^1 is $–CH_2$.

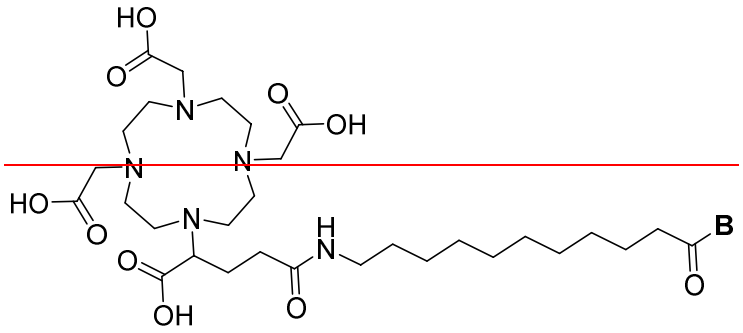
~~9. The compound of any one of claims 1-8, wherein L^2 has n value of 1.~~

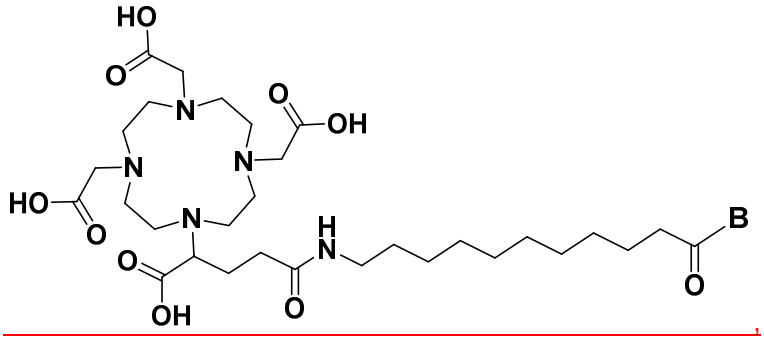
~~10~~9. The compound of claim 1~~any one of claims 1-9~~, wherein the compound is~~ selected from the group consisting of~~:





or





,

wherein variable B is as defined in claim 1.

~~11~~10. The compound of claim 5~~any one of claims 1-10~~, wherein the metal is a radionuclide.

~~12~~11. The compound of claim 10~~11~~, wherein the radionuclide is In^{111}.

~~13~~12. The compound of claim 10~~11~~, wherein the radionuclide is Ga^{68}.

~~14~~13. The compound of claim 1~~any one of claims 1-10~~, wherein the metal is an alpha-emitting radionuclide.

~~15~~14. The compound of claim ~~14~~13, wherein the alpha-emitting radionuclide is Ac^{225} ~~or the progeny (daughter isotopes) thereof~~.

~~16. The compound of any one of claims 1-15, wherein said antibody, or antibody-binding fragment thereof comprises a light chain variable domain comprising at least one, two, or all three complementarity determining regions (CDRs) selected from:~~

~~(a) CDR-L1 comprising the amino acid sequence of SEQ ID NO:1;~~

~~(b) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 2; and~~

~~(c) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 3.~~

~~17. The compound of any one of claims 1-16, wherein said antibody, or antibody-binding fragment thereof comprises a heavy chain variable domain comprising at least one, two, or all three CDRs selected from:~~

~~(a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 5;~~

~~(b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 6; and~~

~~(c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 7.~~

~~18. The compound of any one of claims 1-17, wherein said antibody, or antibody-binding fragment thereof comprises a heavy chain variable domain and a light chain variable domain comprising at least one, two, three, four, five, or all six CDRs selected from:~~

~~(a) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 1;~~

~~(b) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 2;~~

~~(c) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 3;~~

~~(d) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 5;~~

~~(e) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 6; and~~

~~(f) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 7.~~

~~19~~15. The compound of claim 1~~any one of claims 1-18~~, wherein said antibody, or antigen-binding fragment thereof comprises a light chain variable domain comprising~~es~~ the amino acid sequence of SEQ ID NO: 4.

~~20~~16. The compound of claim 1~~any one of claims 1-19~~, wherein said antibody, or antigen-binding fragment thereof comprises a heavy~~light~~ chain variable domain comprising~~es~~ the amino acid sequence of SEQ ID NO: 8.

~~21~~17. The compound of claim 1~~any one of claims 1-20~~, wherein said antibody, or antigen-binding fragment thereof is AVE1642.

~~22. The compound of any one of claims 1-20, wherein said antibody, or antibody-binding fragment thereof, substantially binds to the same epitope as AVE1642.~~

~~23~~18. A pharmaceutical composition comprising a compound of claim 1~~any one of claims 1-22~~ and a pharmaceutically acceptable excipient.

~~24~~19. ~~A method of radiation treatment planning and/or radiation treatment and the method comprising administering to a subject in need thereof~~Use of a compound of claim 1~~compound of any one of claims 1 to 22 or the composition of claim 23~~ in the manufacture of a medicament for radiation treatment planning and/or radiation treatment, wherein a diagnostically effective amount of the medicament is to be administered to a subject in need thereof and/or a therapeutically effective amount of the medicament is to be administered to a subject in need thereof, wherein the compound in each occurrence comprises a radionuclide.

~~25~~20. Use of a compound of claim 13 in the manufacture of a first medicament and use of a compound of claim 1 in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for~~A method of~~ treating cancer, ~~the method comprising administering to a subject in need thereof~~wherein a first dose of the first medicament is to be administered in an amount effective for treating cancer to a subject in need thereof, followed by administration of a second dose of the second medicament~~of a compound of any one of claims 1 to 22 or the composition of claim 23 in an amount effective for radiation treatment planning, followed by administering subsequent doses of a compound of any one of claims 1 to 22 or the composition of claim 30 in a therapeutically effective amount~~, wherein the metal of said metal complex is selected from the group consisting of Bi, Pb, Y, Mn, Cr, Fe, Co, Zn, Ni, Tc, In, Ga, Cu, Re, a lanthanide, and an actinide; or

the metal of said metal complex is a radionuclide selected from the group consisting of ^{47}Sc, ^{55}Co, ^{60}Cu, ^{61}Cu, ^{62}Cu, ^{64}Cu, ^{67}Cu, ^{66}Ga, ^{67}Ga, ^{68}Ga, ^{82}Rb, ^{86}Y, ^{87}Y, ^{90}Y, ^{97}Ru, ^{99m}Tc, ^{105}Rh, ^{109}Pd, ^{111}In, ^{117m}Sn, ^{149}Pm, ^{149}Tb ^{153}Sm, ^{177}Lu, ^{186}Re, ^{188}Re, ^{199}Au, ^{201}Tl, ^{203}Pb, ^{212}Pb, ^{212}Bi, ^{213}Bi, ^{225}Ac, and ^{227}Th.

~~26~~21. The use~~method~~ of claim 20~~25~~, wherein the compound ~~or composition~~ administered in the first dose and the compound ~~or composition~~ administered in the second dose are the same.

~~27~~22. The use~~method~~ of claim 20~~25~~, wherein the compound ~~or composition~~ administered in the first dose and the compound ~~or composition~~ administered in the second dose are different.

~~28~~23. The use~~method~~ of claim 20~~any one of claims 25-27~~, wherein the cancer is a solid tumor or hematologic (liquid) cancer.

~~29~~24. The use~~method~~ claim 23~~28~~, wherein the ~~solid tumor~~ cancer is breast cancer, non-small cell lung cancer, small cell lung cancer, pancreatic cancer, head and neck cancer, prostate cancer, colorectal cancer, sarcoma, adrenocortical carcinoma, Ewing's Sarcoma, multiple myeloma, or acute myeloid leukemia.

~~30~~25. The use~~method~~ of claim 24~~any one of claims 25-29~~, wherein~~further comprising administering~~ an antiproliferative agent, radiation sensitizer, an immunoregulatory or immunomodulatory agent is to be further administered.

~~31~~26. The use~~method~~ of claim 25~~30~~, wherein the medicament ~~compound of any one of claims 1 to 21 or the composition of claim 23~~ and the antiproliferative agent or radiation sensitizer are to be administered within 28 days of each other.

~~32~~27. The use~~method~~ of claim 25~~30~~, wherein the medicament ~~compound of any one of claims 1 to 22 or the composition of claim 23~~ and the~~an~~ immunoregulatory or immunomodulatory agent are to be administered within 90 days of each other.

28. The compound of claim 1, wherein L^3 is C_5-C_{20} polyethylene glycol.

29. The compound of claim 1, wherein said antibody, or antigen-binding fragment thereof comprises a light chain variable domain comprising at least one complementarity determining region (CDR) selected from:

(a) CDR-L1 comprising the amino acid sequence of SEQ ID NO:1;

(b) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 2; and

(c) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 3.

30. The compound of claim 29, wherein said antibody, or antigen-binding fragment thereof comprises a light chain variable domain comprising at least two of said CDRs.

31. The compound of claim 30, wherein said antibody, or antigen-binding fragment thereof comprises a light chain variable domain comprising all three said CDRs.

32. The compound of claim 1, wherein said antibody, or antigen-binding fragment thereof comprises a heavy chain variable domain comprising at least one CDR selected from:

(a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 5;

(b) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 6; and

(c) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 7.

33. The compound of claim 32, wherein said antibody, or antigen-binding fragment thereof comprises a heavy chain variable domain comprising at least two of said CDRs.

34. The compound of claim 33, wherein said antibody, or antigen-binding fragment thereof comprises a heavy chain variable domain comprising all three said CDRs.

35. The compound of claim 1, wherein said antibody, or antigen-binding fragment thereof comprises a heavy chain variable domain and a light chain variable domain, comprising at least one CDR selected from:

(a) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 1;

(b) CDR-L2 comprising the amino acid sequence of SEQ ID NO: 2;

(c) CDR-L3 comprising the amino acid sequence of SEQ ID NO: 3;

(d) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 5;

(e) CDR-H2 comprising the amino acid sequence of SEQ ID NO: 6; and

(f) CDR-H3 comprising the amino acid sequence of SEQ ID NO: 7.

36. The compound of claim 35, wherein said antibody, or antigen-binding fragment thereof comprises a heavy chain variable domain and a light chain variable domain, comprising at least two of said CDRs.

37. The compound of claim 36, wherein said antibody, or antigen-binding fragment thereof comprises a heavy chain variable domain and a light chain variable domain, comprising at least three of said CDRs.

38. The compound of claim 37, wherein said antibody, or antigen-binding fragment thereof comprises a heavy chain variable domain and a light chain variable domain, comprising at least four of said CDRs.

39. The compound of claim 38, wherein said antibody, or antigen-binding fragment thereof comprises a heavy chain variable domain and a light chain variable domain, comprising at least five of said CDRs.

40. The compound of claim 39, wherein said antibody, or antigen-binding fragment thereof comprises a heavy chain variable domain and a light chain variable domain, comprising all six said CDRs.