Androgen depletion therapy (ADT) is the standard treatment with a generally predictable outcome: decline in PSA, a period of stability in which the tumor does not proliferate, followed by rising PSA and regrowth as castration-resistant disease. Historically, ADT has been the standard of care for patients with metastatic prostate cancer.

Kallikrein related peptidase 2 (hK2, HK2) is a trypsin-like enzyme with androgen receptor (AR)-driven expression specific to prostate tissue and prostate cancer. hK2 expression is restricted to the prostate and prostate cancer tissue, however it has recently been demonstrated that hK2 was detectable in breast cancer lines and primary patient samples after appropriate activation of the AR-pathway by steroid hormones (U.S. Pat. Publ. No. 2018/0326102). Retrograde release of catalytically inactive hK2 into the blood occurs when the highly structured organization of the prostate is compromised upon hypertrophy or malignant transformation.

There remains a need for next generation hK2-targeted therapies for therapeutic and diagnostic purposes.

BRIEF SUMMARY ~~OF THE INVENTION~~

~~Embodiments of t~~The present ~~invention~~ disclosure relates to an anti-hk2 radioconjugate comprising an antigen binding domain conjugated with a chelator that binds radiometals for therapeutic use or imaging. According to particular ~~embodiments~~examples, the anti-hK2 radioconjugate comprising an antigen binding domain has a shorter half-life compared to an anti-hK2 radioconjugate comprising a full-length antibody.

In many cases the circulating half-life of immunoglobulin G (IgG) in humans is approximately 10–21 days. The Fc domain in an intact IgG is capable of binding to the neonatal Fc receptor (FcRn), leading to antibody recycling and minimal endosomal degradation. FcRn plays a key role in serum IgG homeostasis as well as in placental transfer of IgG molecules from mother to fetus. Following pinocytosis, the acidic environment of the early endosome allows for binding of IgG (as well as albumin) to FcRn, which provides protection from degradation and facilitates trafficking of IgG back to the extracellular environment, where the molecules dissociate back into circulation upon exposure to physiological pH.

The circulating half-life of an antigen binding domain, such as a Fab, tends to be much shorter than that of an IgG. As the Fab fragment lacks the Fc domain, the FcRn mediated

enhanced half-life mechanism is lacking, thus the Fab alone has a shorter half-life (for example, less than 24 hours, or less than 12 hours, and in some cases about 2-3 hours).

An ~~embodiment~~ aspect of the present disclosure ~~invention~~ provides immunoconjugate comprising a therapeutic moiety conjugated to an antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

According to certain ~~embodiments~~examples, the therapeutic moiety is a cytotoxic agent.

According to certain examples~~embodiments~~, the therapeutic moiety is an imaging agent.

According to certain examples~~embodiments~~, the therapeutic moiety comprises a radiometal. Non-limiting examples of suitable radiometals include ^{225}Ac, ^{177}Lu,^{,32}P, ^{47}Sc, ^{67}Cu, ^{77}As, ^{89}Sr, ^{90}Y, ^{99}Tc, ^{105}Rh, ^{109}Pd, ^{111}Ag, ^{131}I, ^{149}Tb, ^{152}Tb, ^{155}Tb, ^{153}Sm, ^{159}Gd, ^{165}Dy, ^{166}Ho, ^{169}Er, ^{186}Re, ^{188}Re, ^{194}Ir, ^{198}Au, ^{199}Au, ^{211}At, ^{212}Pb, ^{212}Bi, ^{213}Bi, ^{223}Ra, ^{255}Fm, ^{227}Th, ^{177}Lu, ^{62}Cu, ^{64}Cu, ^{67}Ga, ^{68}Ga, ^{86}Y, ^{89}Zr, and ^{111}In.

According to certain examples~~embodiments~~, the therapeutic moiety is a cytotoxic agent comprising ^{225}Ac.

According to certain examples~~embodiments~~, the therapeutic moiety is an imaging agent comprising ^{111}In.

According to certain examples~~embodiments~~, the therapeutic moiety comprises a radiometal complex, wherein the radiometal complex comprises the radiometal bound to a chelator, and wherein the chelator is conjugated to the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

According to certain examples~~embodiments~~, the chelator is 1,4,7,10-tetraazacyclododecane-1,4,7,10,tetraacetic acid (DOTA), S-2-(4-isothiocyanatobenzyl)-1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA), 1,4,8,11-tetraazacyclodocedan-1,4,8,11-tetraacetic acid (TETA), 3,6,9,15-tetraazabicyclo[9.3.1]-pentadeca-1(15),11,13-triene-4-(S)-(4-isothiocyanatobenzyl)-3,6,9-triacetic acid (PCTA), 5-S-(4-aminobenzyl)-1-oxa-4,7,10- triazacyclododecane-4,7,10-tris(acetic acid) (DO3A), or a derivative thereof.

According to certain examples~~embodiments~~, the chelator is DOTA.

According to certain examples~~embodiments~~, the chelator is H_2bp18c6 or a H_2bp18c6 derivative.

According to certain examples~~embodiments~~, the radiometal complex is a radiocomplex of Formula (I-m), or Formula (II-m), or Formula (III-m) as described herein, wherein R_{11} comprises the

antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2) and M is the radiometal.

According to certain examples~~embodiments~~, the radiometal complex is a radiometal complex of Formula (IV-m), or Formula (V-m), or Formula (VI-m) as described herein, wherein R_4 comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2) and M+ is the radiometal.

According to certain examples~~embodiments~~, the therapeutic moiety is an auristatin derivative, such as MMAE (monomethyl auristatin E) or MMAF (monomethyl auristatin F).

According to certain examples~~embodiments~~, the antigen binding domain that binds hK2 is a scFv, a $(scFv)_2$, a Fv, a Fab, a $F(ab')_2$, a Fd, a dAb or a VHH.

According to certain examples~~embodiments~~, the antigen binding domain with binding specificity for hK2 is a Fab.

According to certain examples~~embodiments~~, the antigen binding domain comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NO: 170 (SYYWS), SEQ ID NO: 171 (YIYYSGSTNYNPSLKS), SEQ ID NO: 172 (TTIFGVVTPNFYYGMDV), SEQ ID NO: 173 (RASQGISSYLA), SEQ ID NO: 174 (AASTLQS) and SEQ ID NO: 175 (QQLNSYPLT), respectively.

According to certain examples~~embodiments~~, the antigen binding domain that binds hK2 comprises a VH which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VH of SEQ ID NO: 162 (QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYIYYSGSTNYNPSLKS RVTISVDTSKNQFSLKLSSVTAADTAVYYCAGTTIFGVVTPNFYYGMDVWGQGTTVTVSS), and a VL which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VL of SEQ ID NO: 163 (DIQMTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKFLIYAASTLQSGVPSRFSGS GSGTEFTLTISSLQPEDFATYYCQQLNSYPLTFGGGTKVEIK).

According to certain examples~~embodiments~~, the antigen binding domain that binds hK2 comprises the VH of SEQ ID NO: 162 and the VL of SEQ ID NO: 163.

According to certain examples~~embodiments~~, the antigen binding domain is a Fab that comprises: A) a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ

ID NOs: 170, 171, 172, 173, 174 and 175, respectively; and/or B) a VH of SEQ ID NO: 162 and a VL of SEQ ID NO: 163.

According to certain examples~~embodiments~~, the immunoconjugate is a short half-life immunoconjugate.

According to certain examples~~embodiments~~, a method of treating an hK2-expressing cancer in a subject, comprises administering to the subject a therapeutically effective amount of the immunoconjugate according to any of the foregoing examples~~embodiments~~.

According to certain examples~~embodiments~~, a method of reducing the amount of hK2-expressing tumor cells in a subject, comprises administering to the subject a therapeutically effective amount of the immunoconjugate according to any of the foregoing examples~~embodiments~~. According to another aspect, there is provided use of the immunoconjugate according to any of the foregoing examples in the manufacture of a medicament for reducing the amount of hK2-expressing tumor cells in a subject, wherein the immunoconjugate according to any of the foregoing examples is to be administered to the subject for a time sufficient to reduce the amount of hK2-expressing tumor cells.

According to certain examples~~embodiments~~, a method of treating prostate cancer in a subject comprises administering to the subject a therapeutically effective amount of the immunoconjugate according to any of the foregoing examples~~embodiments~~.

According to another aspect, there is provided use of the immunoconjugate according to any of the foregoing examples in the manufacture of a medicament for treating an hK2-expressing cancer or prostate cancer.

According to certain examples~~embodiments~~, the prostate cancer is relapsed, refractory, malignant or castration resistant prostate cancer, or any combination thereof.

According to certain examples~~embodiments~~, the prostate cancer is metastatic castration-resistant prostate cancer.

According to certain examples~~embodiments~~, a method of detecting the presence of prostate cancer in a subject, comprising administering the immunoconjugate according to any of the foregoing examples ~~embodiments~~ to a subject suspected to have prostate cancer and visualizing the biological structures to which the conjugate is bound (e.g., by computerized tomography or positron emission tomography), thereby detecting the presence of prostate cancer, wherein the immunoconjugate preferably comprises an imaging agent, such as 111-In or 64-Cu.

According to another aspect, there is provided a method of detecting the presence of prostate cancer in a subject, comprising visualizing, after the immunoconjugate according to any of the foregoing examples had been administered to the subject, the biological structures to which the immunoconjugate according to any of the foregoing examples is bound thereby detecting the presence of prostate cancer. According to certain examples~~embodiments~~, the method comprises conjugating the therapeutic moiety to the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

According to another aspect, there is provided a method of making an immunoconjugate according to any of the foregoing examples comprising: conjugating the therapeutic moiety to the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

According to ~~certain embodiments~~another aspect, there is provided a method of making a radioimmunoconjugate ~~as described herein comprises~~ comprising binding a radiometal to a chelator that is conjugated to an antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

According to certain examples~~embodiments~~, a short half-life radioimmunoconjugate comprises a radiometal complex, wherein the radiometal complex comprises ^{225}Ac bound to a chelator,

and wherein the chelator is conjugated to a Fab with binding specificity for hK2, said Fab comprising: a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively. According to certain examples~~embodiments~~, said Fab comprises a VH of SEQ ID NO: 162 and a VL of SEQ ID NO: 163.

DETAILED DESCRIPTION OF THE DRAWINGS

The foregoing summary, as well as the following detailed description of the invention, will be better understood when read in conjunction with the appended drawings. It should be understood that the invention is not limited to the precise embodiments shown in the drawings.

In the drawings:

FIG. 1 shows cell binding and internalization of an immunoconjugate of the present invention, comprising the KL2B30 Fab (identified as KL2B997) conjugated to MMAF (monomethyl auristatin F), in hK2-expressing VCaP cells.

FIG. 2 shows amino acid sequences (heavy chain and light chain sequences) of KL2B997 and KL2B1251. KL2B997 has a His-tag and a sortase tag (underlined in FIG. 2) on the heavy chain, and KL2B1251 is tagless.

DETAILED DESCRIPTION OF THE INVENTION

Various publications, articles and patents are cited or described in the background and throughout the specification; each of these references is herein incorporated by reference in its entirety. Discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is for the purpose of providing context for the invention. Such discussion is not an admission that any or all of these matters form part of the prior art with respect to any inventions disclosed or claimed.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning commonly understood to one of ordinary skill in the art to which this invention pertains. Otherwise, certain terms cited herein have the meanings as set in the specification. All patents, published patent applications and publications cited herein are incorporated by reference as if set forth fully herein

As used herein, the conjunctive term “and/or” between multiple recited elements is understood as encompassing both individual and combined options. For instance, where two

CLAIMS

What is claimed is:

1. An immunoconjugate comprising: a therapeutic moiety conjugated to an antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

2. The immunoconjugate according to claim 1, wherein the therapeutic moiety is a cytotoxic agent or an imaging agent.

~~3. The immunoconjugate according to claim 1, wherein the therapeutic moiety is an imaging agent.~~

~~4.~~3. The immunoconjugate according to ~~any of~~ claim~~s~~ 1~~-3~~ or 2, wherein the therapeutic moiety comprises a radiometal, preferably the radiometal is selected from the group consisting of ^{225}Ac, ^{177}Lu, ^{32}P, ^{47}Sc, ^{67}Cu, ^{77}As, ^{89}Sr, ^{90}Y, ^{99}Tc, ^{105}Rh, ^{109}Pd, ^{111}Ag, ^{131}I, ^{149}Tb, ^{152}Tb, ^{155}Tb, ^{153}Sm, ^{159}Gd, ^{165}Dy, ^{166}Ho, ^{169}Er, ^{186}Re, ^{188}Re, ^{194}Ir, ^{198}Au, ^{199}Au, ^{211}At, ^{212}Pb, ^{212}Bi, ^{213}Bi, ^{223}Ra, ^{255}Fm, ^{227Th}, ^{177}Lu, ^{62}Cu, ^{64}Cu, ^{67}Ga, ^{68}Ga, ^{86}Y, ^{89}Zr, and ^{111}In.

~~5. The immunoconjugate according to claim 4, wherein the radiometal is selected from the group consisting of ^{225}Ac, ^{177}Lu, ^{32}P, ^{47}Sc, ^{67}Cu, ^{77}As, ^{89}Sr, ^{90}Y, ^{99}Tc, ^{105}Rh, ^{109}Pd, ^{111}Ag, ^{131}I, ^{149}Tb, ^{152}Tb, ^{155}Tb, ^{153}Sm, ^{159}Gd, ^{165}Dy, ^{166}Ho, ^{169}Er, ^{186}Re, ^{188}Re, ^{194}Ir, ^{198}Au, ^{199}Au, ^{211}At, ^{212}Pb, ^{212}Bi, ^{213}Bi, ^{223}Ra, ^{255}Fm, ^{227Th}, ^{177}Lu, ^{62}Cu, ^{64}Cu, ^{67}Ga, ^{68}Ga, ^{86}Y, ^{89}Zr, and ^{111}In.~~

~~6.~~4. The immunoconjugate of claim 1, wherein the therapeutic moiety is a cytotoxic agent comprising ^{225}Ac or an imaging agent comprising ^{111}In.

~~7. The immunoconjugate of claim 1, wherein the therapeutic moiety is an imaging agent comprising ^{111}In.~~

~~8.~~5. The immunoconjugate according to ~~any of~~ claim~~s~~ ~~4-7~~3 or 4, wherein the therapeutic moiety comprises a radiometal complex, wherein the radiometal complex comprises the radiometal bound to a chelator, and wherein the chelator is conjugated to the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

~~9.~~6. The immunoconjugate according to claim 5~~8~~, wherein the chelator is 1,4,7,10-tetraazacyclododecane-1,4,7,10,tetraacetic acid (DOTA), S-2-(4-isothiocyanatobenzyl)-1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA), 1,4,8,11-t~~e~~traazacyclodocedan-1,4,8,11-tetraacetic acid (TETA), 3,6,9,15-tetraazabicyclo[9.3.1]-pentadeca-1(15),11,13-triene-4-(S)-(4-isothiocyanatobenzyl)-3,6,9-triacetic acid (PCTA), 5-S-(4-aminobenzyl)-1-oxa-4,7,10-

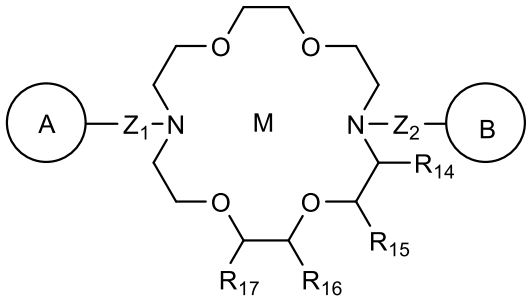
triazacyclododecane-4,7,10-tris(acetic acid) (DO3A), or a derivative thereof; H_2bp18c6 or a H_2bp18c6 derivative.

~~10. The immunoconjugate according to claim 8, wherein the chelator is DOTA.~~

~~11. The immunoconjugate according to claim 8, wherein the chelator is H_2bp18c6 or a H_2bp18c6 derivative.~~

~~12.~~7. The immunoconjugate according to claim ~~8~~5, wherein the radiometal complex is a radiometal complex of Formula (I-m), or Formula (II-m), or Formula (III-m),

wherein the radiometal complex of Formula (I-m) has the following structure:



(I-m)

wherein:

M is the radiometal, preferably an alpha-emitting radiometal ion, and more preferably actinium-225 (^{225}Ac);

each of ring A and ring B is independently a 6-10 membered aryl or a 5-10 membered heteroaryl, wherein each of ring A and ring B is optionally substituted with one or more substituents independently selected from the group consisting of halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, $-OR_{13}$, $-SR_{13}$, , $-(CH_2)_pCOOR_{13}$, $-OC(O)R_{13}$, $-N(R_{13})_2$, $-CON(R_{13})_2$, $-NO_2$, -CN $-OC(O)N(R_{13})_2$, and X;

each of Z_1 and Z_2 is independently $–(C(R_{12})_2)_m$- or $–(CH_2)_n$-$C(R_{12})(X)$-$(CH_2)_n$-;

each X is independently -L_1-R_{11};

each n is independently 0, 1, 2, 3, 4, or 5;

each m is independently 1, 2, 3, 4, or 5;

each p is independently 0 or 1;

L_1 is absent or a linker;

R_{11} comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2);

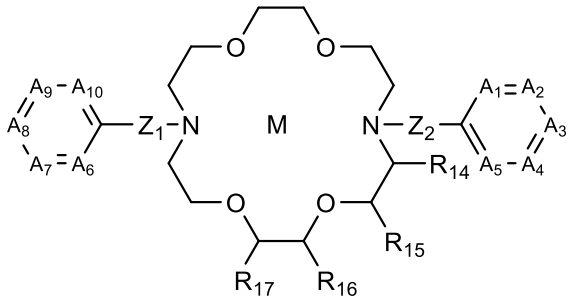
each R_{12} is independently hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl;

each R_{13} is independently hydrogen or alkyl;

each of R_{14}, R_{15}, R_{16}, and R_{17} is independently hydrogen, alkyl, or X,

or alternatively R_{14} and R_{15} and/or R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring optionally substituted with X; provided that the radiometal complex comprises at least one X, and when X is present on ring A or ring B, L_1 is a linker or at least one of R_{12} and R_{14}-R_{17} is not hydrogen;

wherein the radiometal complex of Formula (II-m) has the following structure:



(II-m)

wherein:

M is the radiometal, preferably an alpha-emitting radiometal ion, and more preferably actinium-225 (^{225}Ac);

A_1 is N or CR_1 or is absent;

A_2 is N or CR_2;

A_3 is N or CR_3;

A_4 is N or CR_4;

A_5 is N or CR_5;

A_6 is N or CR_6 or is absent;

A_7 is N or CR_7;

A_8 is N or CR_8;

A_9 is N or CR_9;

A_{10} is N or CR_{10};

provided that no more than three of A_1, A_2, A_3, A_4, and A_5 are N, and no more than three of A_6, A_7, A_8, A_9, and A_{10} are N;

each of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} is independently selected from the group consisting of hydrogen, halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, $-OR_{13}$, $-SR_{13}$, $-(CH_2)_pCOOR_{13}$, $-OC(O)R_{13}$, $-N(R_{13})_2$, $-CON(R_{13})_2$, $-NO_2$, -CN $-OC(O)N(R_{13})_2$, and -X,

or, alternatively, any two directly adjacent R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} are taken together with the atoms to which they are attached to form a five or six-membered substituted or unsubstituted carbocyclic or nitrogen-containing ring;

each of Z_1 and Z_2 is independently $–(C(R_{12})_2)_m-$ or $–(CH_2)_n-C(R_{12})(X)-(CH_2)_n-$;

each X is independently $-L_1-R_{11}$;

each n is independently 0, 1, 2, 3, 4, or 5;

each m is independently 1, 2, 3, 4, or 5;

each p is independently 0 or 1;

L_1 is absent or a linker;

R_{11} comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2);

each R_{12} is independently hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl;

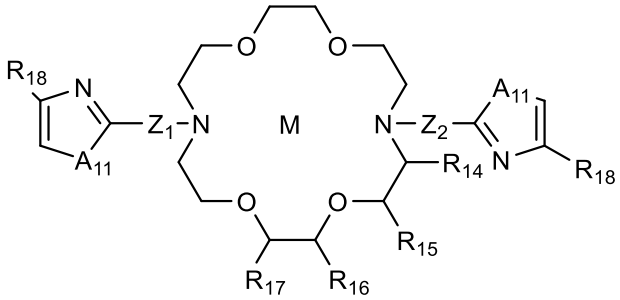
each R_{13} is independently hydrogen or alkyl;

each of R_{14}, R_{15}, R_{16}, and R_{17} is independently hydrogen, alkyl, or X,

or alternatively R_{14} and R_{15} and/or R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring optionally substituted with X;

provided that the radiometal complex comprises at least one X, and when any one of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} is X, then L_1 is a linker or at least one of R_{12} and R_{14}-R_{17} is not hydrogen;

wherein the radiometal complex of Formula (III-m) has the following structure:



(III-m)

wherein:

M is the radiometal, preferably an alpha-emitting radiometal ion, and more preferably actinium-225 (^{225}Ac);

each A_{11} is independently O, S, NMe, or NH;

each of Z_1 and Z_2 is independently $–(C(R_{12})_2)_m$- or $–(CH_2)_n$-$C(R_{12})(X)$-$(CH_2)_n$-;

each X is independently -L_1-R_{11};

each n is independently 0, 1, 2, 3, 4, or 5;

each m is independently 1, 2, 3, 4, or 5;

each p is independently 0 or 1;

L_1 is absent or a linker;

R_{11} comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2);

each R_{12} is independently hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl;

each R_{13} is independently hydrogen or alkyl;

each of R_{14}, R_{15}, R_{16}, and R_{17} is independently hydrogen, alkyl, or X,

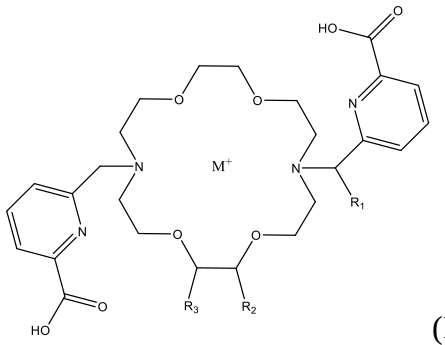
or alternatively R_{14} and R_{15} and/or R_{16} and R_{17} are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl ring optionally substituted with X; and

each R_{18} is independently selected from the group consisting of hydrogen, halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, -OR_{13}, -SR_{13}, , -$(CH_2)_p$$COOR_{13}$, -$OC(O)R_{13}$, -$N(R_{13})_2$, -$CON(R_{13})_2$, -$NO_2$, -CN -$OC(O)N(R_{13})_2$, and -X,

provided that the radiometal complex comprises at least one X, and when R_{18} is X, then L_1 is a linker or at least one of R_{12} and R_{14}-R_{17} is not hydrogen.

~~13.~~8. The immunoconjugate according to claim ~~8~~5, wherein the radiometal complex is a radiometal complex of Formula (IV-m), or Formula (V-m), or Formula (VI-m),

wherein the radiometal complex of Formula (IV-m) has the following structure:



(IV-m)

or a pharmaceutically acceptable salt thereof, wherein:

M^+ is the radiometal, preferably selected from the group consisting of actinium-225(^{225}Ac), radium-223 (^{233}Ra), bismuth-213 (^{213}Bi), lead-212 (^{212}Pb(II) and/or ^{212}Pb(IV)), terbium-149 (^{149}Tb), terbium-152 (^{152}Tb), terbium-155 (^{155}Tb),fermium-255 (^{255}Fm), thorium-227 (^{227}Th), thorium-226 ($^{226}Th^{4+}$), astatine-211 (^{211}At), cerium-134 (^{134}Ce), neodymium-144 (^{144}Nd), lanthanum-132 (^{132}La), lanthanum-135 (^{135}La) and uranium-230 (^{230}U);

R_1 is hydrogen and R_2 is $-L_1-R_4$;

alternatively, R_1 is $-L_1-R_4$ and R_2 is hydrogen;

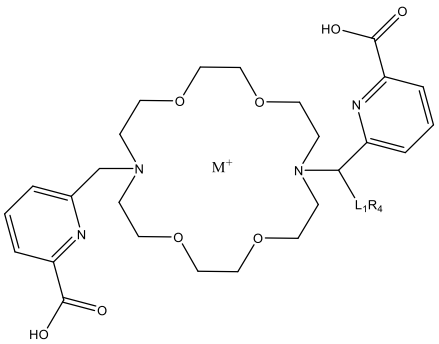
R_3 is hydrogen;

alternatively, R_2 and R_3 are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered cycloalkyl, wherein the 5- or 6-membered cycloalkyl is optionally substituted with $-L_1-R_4$;

L_1 is absent or a linker;

R_4 comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2);

wherein the radiometal complex of Formula (V-m) has the following structure:



(V-m)

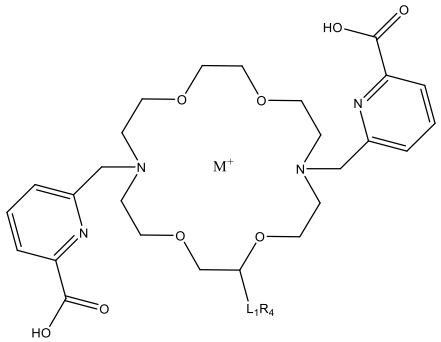
or a pharmaceutically acceptable salt thereof, wherein:

M^+ is the radiometal, preferably selected from the group consisting of actinium-225(^{225}Ac), radium-223 (^{233}Ra), bismuth-213 (^{213}Bi), lead-212 (^{212}Pb(II) and/or ^{212}Pb(IV)), terbium-149 (^{149}Tb), terbium-152 (^{152}Tb), terbium-155 (^{155}Tb),fermium-255 (^{255}Fm), thorium-227 (^{227}Th), thorium-226 ($^{226}Th^{4+}$), astatine-211 (^{211}At), cerium-134 (^{134}Ce), neodymium-144 (^{144}Nd), lanthanum-132 (^{132}La), lanthanum-135 (^{135}La) and uranium-230 (^{230}U);

L_1 is absent or a linker;

R_4 comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2);

wherein the radiometal complex of Formula (VI-m) has the following structure:



(VI-m)

or a pharmaceutically acceptable salt thereof, wherein:

M^+ is the radiometal, preferably selected from the group consisting of actinium-225(^{225}Ac), radium-223 (^{233}Ra), bismuth-213 (^{213}Bi), lead-212 (^{212}Pb(II) and/or ^{212}Pb(IV)), terbium-149 (^{149}Tb), terbium-152 (^{152}Tb), terbium-155 (^{155}Tb),fermium-255 (^{255}Fm), thorium-227 (^{227}Th), thorium-226 ($^{226}Th^{4+}$), astatine-211 (^{211}At), cerium-134

(^{134}Ce), neodymium-144 (^{144}Nd), lanthanum-132 (^{132}La), lanthanum-135 (^{135}La) and uranium-230 (^{230}U);

L_1 is absent or a linker; and

R_4 comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

~~14.~~9. The immunoconjugate of claim 1, wherein the therapeutic moiety is an auristatin derivative.

~~15.~~10. The immunoconjugate of claim ~~14~~9, wherein the therapeutic moiety is MMAE (monomethyl auristatin E) or MMAF (monomethyl auristatin F).

~~16. The immunoconjugate of claim 14, wherein the therapeutic moiety is MMAF (monomethyl auristatin F).~~

~~17.~~11. The immunoconjugate according to any of claims 1-~~16~~10, wherein the antigen binding domain with binding specificity for hK2~~that binds hK2~~:

(i) is a scFv, a $(scFv)_2$, a Fv, a Fab, a $F(ab')_2$, a Fd, a dAb or a VHH;

(ii) comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively;

(iii) comprises a VH which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VH of SEQ ID NO: 162 and a VL which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VL of SEQ ID NO: 163;

(iv) comprises the VH of SEQ ID NO: 162 and the VL of SEQ ID NO: 163; and/or

(v) is a Fab that comprises:

a. a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively; and/or

b. a VH of SEQ ID NO: 162 and a VL of SEQ ID NO: 163.

~~18. The immunoconjugate according to any of claims 1-16, wherein the antigen binding domain with binding specificity for hK2 is a Fab.~~

~~19. The immunoconjugate according to any of claims 1-18, wherein the antigen binding domain comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively.~~

~~20. The immunoconjugate according to any of claims 1-19, wherein the antigen binding domain that binds hK2 comprises a VH which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VH of SEQ ID NO: 162 and a VL which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VL of SEQ ID NO: 163.~~

~~21. The immunoconjugate according to any of claims 1-19, wherein the antigen binding domain that binds hK2 comprises the VH of SEQ ID NO: 162 and the VL of SEQ ID NO: 163.~~

~~22. The immunoconjugate according to any of claims 1-18, wherein the antigen binding domain is a Fab that comprises:~~

~~a. a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively; and/or~~

~~b. a VH of SEQ ID NO: 162 and a VL of SEQ ID NO: 163.~~

~~23.~~12. The immunoconjugate according to any of claims 1-~~22~~11, wherein the immunoconjugate is a short half-life immunoconjugate.

~~24.~~13. Use of the immunoconjugate according to any of claims 1-12 in the manufacture of a medicament for ~~A method of~~ treating an hK2-expressing cancer or prostate cancer ~~in a subject, comprising administering to the subject a therapeutically effective amount of the immunoconjugate according to any of claims 1-23~~.

~~25.~~14. Use of the immunoconjugate according to any of claims 1-12 in the manufacture of a medicament for ~~A method of~~ reducing the amount of hK2-expressing tumor cells in a subject, ~~comprising administering~~ wherein the immunoconjugate according to any of claims 1-~~23~~12 is to be administered to the subject for a time sufficient to reduce the amount of hK2-expressing tumor cells.

~~26. A method of treating prostate cancer in a subject, comprising administering to the subject a therapeutically effective amount of the immunoconjugate according to any of claims 1-23.~~

~~27.~~15. The ~~method~~ use of claim ~~26~~13, wherein the prostate cancer is relapsed, refractory, malignant or castration resistant prostate cancer, or any combination thereof or is metastatic castration-resistant prostate cancer.

~~28. The method of claim 26, wherein the prostate cancer is metastatic castration-resistant prostate cancer.~~

~~29.~~16. A method of detecting the presence of prostate cancer in a subject, comprising ~~administering the immunoconjugate according to any of claims 1-23 to a subject suspected to have prostate cancer and~~ visualizing, after the immunoconjugate according to any of claims 1-12 had been administered to the subject, the biological structures to which the immunoconjugate according to any of claims 1-12 is bound thereby detecting the presence of prostate cancer.

~~30.~~17. A method of making an immunoconjugate according to any of claims 1-~~23~~ 12 comprising: conjugating the therapeutic moiety to the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

~~31.~~18. A method of making a radioimmunoconjugate comprising binding a radiometal to a chelator that is conjugated to an antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

~~32.~~19. The method of claim ~~31~~18, wherein the chelator is:

(i) DOTA;

(ii) H_2bp18c6 or a H_2bp18c6 derivative;

(iii) selected from the group consisting of chelators of Formula (I), Formula (II) and Formula (III) as described herein, wherein R_{11} comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2); or

(iv) selected from the group consisting of chelators of Formula (IV), Formula (V) and Formula (VI) as described herein, wherein R_4 comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).

~~33. The method of claim 31, wherein the chelator is H_2bp18c6 or a H_2bp18c6 derivative.~~

~~34. The method of claim 31, wherein the chelator is selected from the group consisting of chelators of Formula (I), Formula (II) and Formula (III) as described herein, wherein R_{11} comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2)~~

~~35. The method of claim 31, wherein the chelator is selected from the group consisting of chelators of Formula (IV), Formula (V) and Formula (VI) as described herein,~~

~~wherein R_4 comprises the antigen binding domain with binding specificity for kallikrein related peptidase 2 (hK2).~~

~~36.~~20. The method according to ~~any of~~ claim~~s 31~~18~~-35~~ or 19, wherein the antigen binding domain with binding specificity for ~~that binds~~ hK2:

(i) is a scFv, a $(scFv)_2$, a Fv, a Fab, a $F(ab')_2$, a Fd, a dAb or a VHH;

(ii) comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively;

(iii) comprises a VH which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VH of SEQ ID NO: 162 and a VL which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VL of SEQ ID NO: 163;

(iv) comprises the VH of SEQ ID NO: 162 and the VL of SEQ ID NO: 163; and/or

(v) a Fab that comprises:

a. a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively; and/or

b. a VH of SEQ ID NO: 162 and a VL of SEQ ID NO: 163.

~~37. The method according to any of claims 31-35, wherein the antigen binding domain that binds hK2 is a Fab.~~

~~38. The method according to any of claims 31-37, wherein the antigen binding domain comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively.~~

~~39. The method according to any of claims 31-38, wherein the antigen binding domain that binds hK2 comprises a VH which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VH of SEQ ID NO: 162 and a VL which is at least 80% (*e.g.* at least 85%, at least 90%, at least 95%, at least 99% or 100%) identical to the VL of SEQ ID NO: 163.~~

~~40. The method according to any of claims 31-38, wherein the antigen binding domain that binds hK2 comprises the VH of SEQ ID NO: 162 and the VL of SEQ ID NO: 163.~~

~~41. The method according to any of claims 31-37, wherein the antigen binding domain is a Fab that comprises:~~

~~a. a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 170, 171, 172, 173, 174 and 175, respectively; and/or~~

~~b. a VH of SEQ ID NO: 162 and a VL of SEQ ID NO: 163~~