CLAIMS

1. An alkaline phosphatase, placental type (ALPP) and/or alkaline phosphatase, germ cell type (ALPPL2) specific antigen binding molecule comprising an amino acid sequence represented by the formula (I):

FW1-CDR1-FW2-CDR2-FW3-CDR3-FW4 (I)

in which

FW1 is a framework region;

CDR1 is a CDR sequence;

FW2 is a framework region;

CDR2 is a CDR sequence;

FW3 is a framework region;

CDR3 is a CDR sequence;

FW4 is a framework region, in which

CDR1 is a CDR sequence having an amino acid sequence of SEQ ID NO: 12, CDR2 is a CDR sequence having an amino acid sequence of SEQ ID NO: 7, and CDR3 is a CDR sequence having an amino acid sequence of SEQ ID NO: 2; or

CDR1 is a CDR sequence having an amino acid sequence of SEQ ID NO: 15, CDR2 is a CDR sequence having an amino acid sequence of SEQ ID NO: 10, and CDR3 is a CDR sequence having an amino acid sequence of SEQ ID NO: 5; or

CDR1 is a CDR sequence having an amino acid sequence of SEQ ID NO: 11, CDR2 is a CDR sequence having an amino acid sequence of SEQ ID NO: 6, and CDR3 is a CDR sequence having an amino acid sequence of SEQ ID NO: 1; or

CDR1 is a CDR sequence having an amino acid sequence of SEQ ID NO: 13, CDR2 is a CDR sequence having an amino acid sequence of SEQ ID NO: 8, and CDR3 is a CDR sequence having an amino acid sequence of SEQ ID NO: 3; and/or

CDR1 is a CDR sequence having an amino acid sequence of SEQ ID NO: 14, CDR2 is a CDR sequence having an amino acid sequence of SEQ ID NO: 9, and CDR3 is a CDR sequence having an amino acid sequence of SEQ ID NO: 4.

2. An ALPP and/or ALPPL2 specific antigen binding molecule according to Claim 1, having an amino acid sequence having at least 70% identity to any one of SEQ ID NOs: 28, 34, 17, 30 or 31.

3. A recombinant fusion protein comprising an ALPP and/or ALPPL2 specific antigen binding molecule according to Claim 1 or 2.

4. A recombinant fusion protein according to Claim 3, in which

(a) the ALPP and/or ALPPL2 specific antigen binding molecule is fused to one or more biologically active proteins via one or more linker domains, optionally in which the linker is selected from the group consisting of G_4S (SEQ ID NO: 236) and $[G_4S]_3$ (SEQ ID NO: 237);

(b) the at least one biologically active molecule is an immunoglobulin, an immunoglobulin Fc region, a fragment of an immunoglobulin Fc region, an Fc heavy chain, a CH2 region, a CH3 region, an immunoglobulin Fab region, a Fab', a Fv, a Fv-Fc, a single chain Fv (scFv), scFv-Fc, (scFv)2, a diabody, a triabody, a tetrabody, a bispecific t-cell engager, an intein, a VNAR domain, a single domain antibody (sdAb), a VH domain, or a scaffold protein (affibodies, centyrins, darpins etc.);

(c) the at least one biologically active protein is an immunoglobulin Fc region or fragment thereof;

(d) the recombinant fusion protein has an amino acid sequence according to SEQ ID NO: 87 to 96;

(e) the immunoglobulin Fc region comprises a mutation to Cys (C), optionally in which the C mutation is at position S239 and/or at position S442;

(f) the recombinant fusion protein has an amino acid sequence of SEQ ID NO: 97 to 121;

(g) the fragment of an immunoglobulin Fc region is engineered to dimerize with a second fragment of an immunoglobulin Fc region;

(h) one or more residues of the first fragment of an immunoglobulin Fc region comprise one or more amino acid substitutions suitable for knobs-in-holes (KIH) dimerization with the second fragment of an immunoglobulin Fc region, and in which one or more residues of the second fragment of an immunoglobulin Fc region comprise

one or more amino acid substitutions suitable for knobs-in-holes (KIH) dimerization with the first fragment of an immunoglobulin Fc region;

(i) the fragment of an immunoglobulin Fc region comprises a T366Y substitution or a Y407T substitution; and/or

(j) the recombinant fusion protein has an amino acid sequence of SEQ ID NO: 188 to 208 or SEQ ID NO: 127 to 186.

5. A recombinant fusion protein dimer comprising

(a) a first recombinant fusion protein according to Claim 3 or 4; and

(b) a second recombinant fusion protein according to Claim 3 or 4.

6. A recombinant fusion protein dimer according to Claim 5 comprising any one or any two of SEQ ID NOs 87 to 186 or 188 to 208, optionally in which;

(a) the first recombinant fusion protein comprises a sequence according to SEQ ID NO: 138 (D10-hFc (long linker) S239C + T366Y), and

(b) the second recombinant fusion protein comprises a sequence according to SEQ ID NO: 131 (F05-hFc (long linker) S239C + Y407T);

(a) the first recombinant fusion protein comprises a sequence according to SEQ ID NO: 178 (D10-hFc S239C & S442C + T366Y), and

(b) the second recombinant fusion protein comprises a sequence according to SEQ ID NO: 171 (F05-hFc S239C & S442C + Y407T);

(a) the first recombinant fusion protein comprises a sequence according to SEQ ID NO: 138 (D10-hFc (long linker) S239C + T366Y), and

(b) the second recombinant fusion protein comprises a sequence according to SEQ ID NO: 129 (E06-hFc (long linker) S239C + Y407T);

(a) the first recombinant fusion protein comprises a sequence according to SEQ ID NO: 138 (D10-hFc (long linker) S239C + T366Y), and

(b) the second recombinant fusion protein comprises a sequence according to SEQ ID NO: 130 (E10-hFc (long linker) S239C + Y407T);

(a) the first recombinant fusion protein comprises a sequence according to SEQ ID NO: 137 (A06-hFc S239C T366Y), and

(b) the second recombinant fusion protein comprises a sequence according to SEQ ID NO: 131 (F05-hFc (long linker) S239C + Y407T);

(a) the first recombinant fusion protein comprises a sequence according to SEQ ID NO: 143 (D10-hFc (short linker) S239C + T366Y), and

(b) the second recombinant fusion protein comprises a sequence according to SEQ ID NO: 134 (E06-hFc (short linker) S239C + Y407T);

(a) the first recombinant fusion protein comprises a sequence according to SEQ ID NO: 143 (D10-hFc (short linker) S239C + T366Y), and

(b) the second recombinant fusion protein comprises a sequence according to SEQ ID NO: 135 (E10-hFc (short linker) S239C Y407T);

(a) the first recombinant fusion protein comprises a sequence according to SEQ ID NO: 143 (D10-hFc (short linker) S239C + T366Y), and

(b) the second recombinant fusion protein comprises a sequence according to SEQ ID NO: 136 (F05-hFc (short linker) S239C + Y407T);

(a) the first recombinant fusion protein comprises a sequence according to SEQ ID NO: 178 (D10-hFc S239C & S442C T366Y), and

(b) the second recombinant fusion protein comprises a sequence according to SEQ ID NO: 169 (E06-hFc S239C & S442C + Y407T);

(a) the first recombinant fusion protein comprises a sequence according to SEQ ID NO: 178 (D10-hFc S239C & S442C + T366Y), and

(b) the second recombinant fusion protein comprises a sequence according to SEQ ID NO: 170 (E10-hFc S239C & S442C + Y407T);

(a) the first recombinant fusion protein comprises a sequence according to SEQ ID NO: 177 (A06-hFc S239C & S442C + T366Y), and

(b) the second recombinant fusion protein comprises a sequence according to SEQ ID NO: 171 (F05-hFc S239C & S442C + Y407T);

(a) the first recombinant fusion protein comprises a sequence according to SEQ ID NO: 183 (D10-hFc (short linker) S239C & S442C + T366Y), and

(b) the second recombinant fusion protein comprises a sequence according to SEQ ID NO: 174 (E06-hFc (short linker) S239C & S442C + Y407T);

(a) the first recombinant fusion protein comprises a sequence according to SEQ ID NO: 183 (D10-hFc (short linker) S239C & S442C + T366Y), and

(b) the second recombinant fusion protein comprises a sequence according to SEQ ID NO: 175 (E10-hFc (short linker) S239C & S442C + Y407T); or

(a) the first recombinant fusion protein comprises a sequence according to SEQ ID NO: 183 (D10-hFc (short linker) S239C & S442C + T366Y), and

(b) the second recombinant fusion protein comprises a sequence according to SEQ ID NO: 176 (F05-hFc (short linker) S239C & S442C + Y407T).

7. A target-binding molecule-drug conjugate, comprising

(a) an ALPP and/or ALPPL2 specific antigen binding molecule according to Claim 1 or 2, a recombinant fusion protein according to Claim 3 or 4, or a recombinant fusion protein dimer according to Claim 5 or 6; and

(b) at least one toxin, cytotoxic or cytostatic agent.

8. A target-binding molecule-drug conjugate according to Claim 7, in which the ALPP and/or ALPPL2 specific antigen binding molecule is conjugated to the cytotoxic or cytostatic agent via a linker, and/or in which (b) is a toxin selected from the group consisting of:

auristatins;

anthracyclines, preferably PNU-derived anthracyclines;

maytansinoids;

amanitin derivatives, preferably α-amanitin derivatives;

calicheamicins;

tubulysins;

duocarmycins;

radioisotopes - such as an alpha-emitting radionuclide, such as 227 Th and 225 Ac label;

liposomes comprising a toxic payload;

protein toxins;

taxanes;

pyrrolbenzodiazepines and dimers thereof;

indolinobenzodiazepine pseudodimers;

spliceosome inhibitors;

CDK11 inhibitors;

nicotinamide phosphoribosyltransferase inhibitors (NAMPTi);

Pyridinobenzodiazepines and dimers thereof;

Cyclopropapyrroloindole (CPI), cyclopropabenzindole (CBI) or cyclopropathienoindole (CTI) and optionally dimers thereof; and

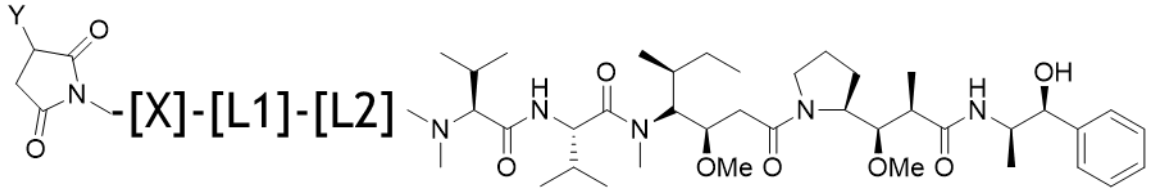
Irinotecan or exatecan and their derivatives.

9. A target-binding molecule-drug conjugate according to Claim 7 or 8,

(i) in which the toxin is an auristatin, optionally in which the toxin is a monomethyl auristatin or monomethyl auristatin E;

(ii) in which (b) is an a MMAE derivative,

in which the target-binding molecule-drug conjugate has the structure of formula (VI):



(VI)

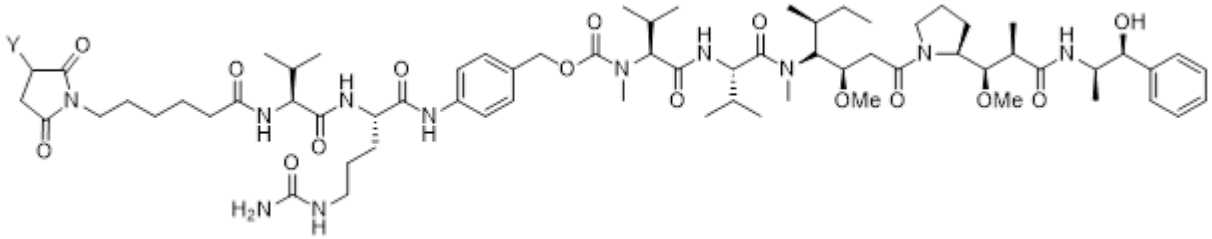
[X] is an optional spacer selected from the group comprising substituted or unsubstituted alkyl groups, substituted or unsubstituted heteroalkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heteroaryl groups, one or more heteroatoms, polyethylene glycol, or a combination thereof;

[L1] and [L2] are optional linkers selected from the group consisting of valine (Val), citrulline (Cit), alanine (Ala), asparagine (Asn), a peptide, a dipeptide, a tripeptide, -

(CH2)n-, -(CH2CH2O)n-, p-aminobenzyloxycarbonyl (PAB), Val-Cit-PAB, Val-Ala-PAB, Ala-Ala-Asn-PAB, Val-Ala, Asn-Ala, any amino acid, D-amino acids, Phe-Lys-PAB, and combinations thereof; and

Y comprises an ALPP and/or ALPPL2 specific antigen binding molecule or recombinant fusion protein according to any of Claims 1 to 6, optionally in which (b) is an a MMAE derivative,

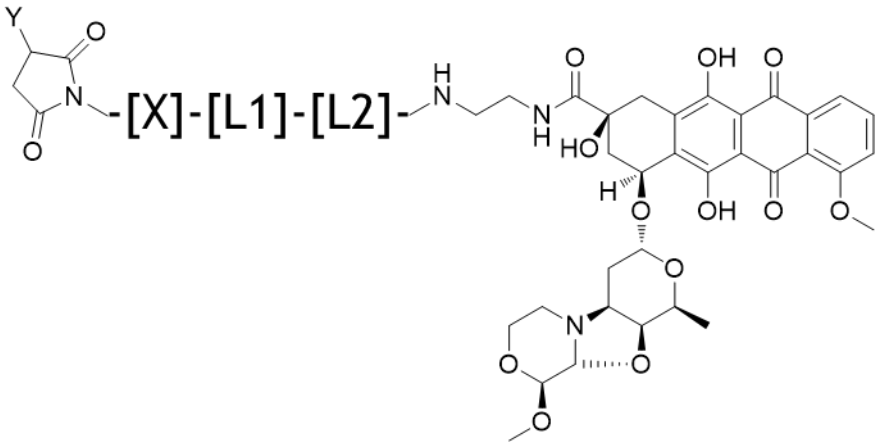
in which the target-binding molecule-drug conjugate has the structure of formula (VII):



(VII);

(iii) comprising (b) an anthracycline (PNU) derivative,

in which the target-binding molecule-drug conjugate has the structure of formula (III):



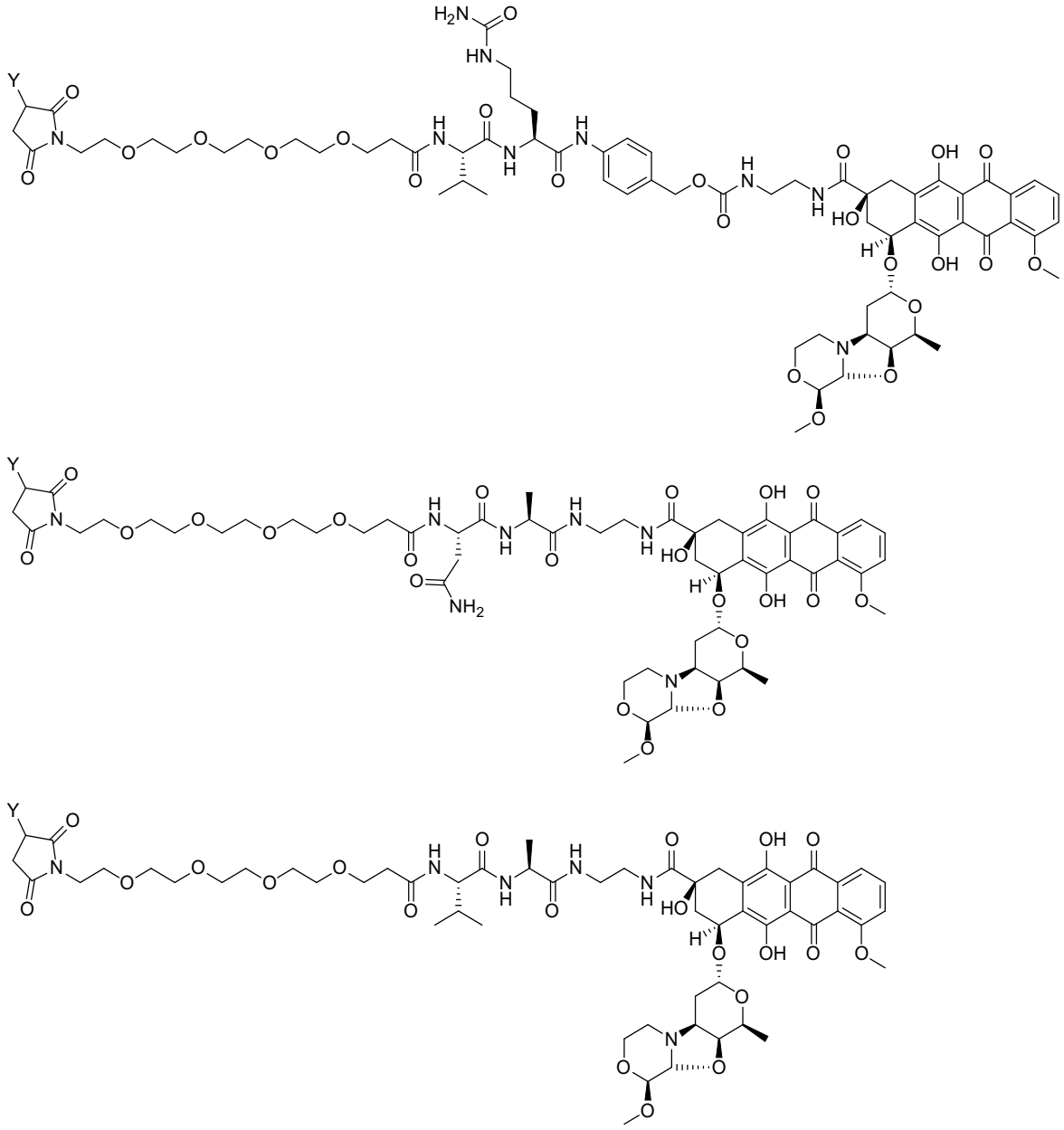
(III)

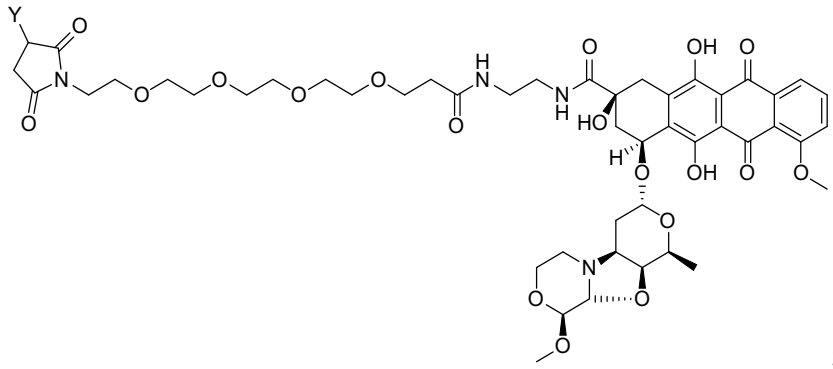
in which [X] is an optional spacer selected from the group comprising substituted or unsubstituted alkyl groups, substituted or unsubstituted heteroalkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heteroaryl groups, one or more heteroatoms, polyethylene glycol, or a combination thereof;

[L1] and [L2] are optional linkers selected from the group consisting of valine (Val), citrulline (Cit), alanine (Ala), asparagine (Asn), a peptide, $-(CH_2)_n-$, $-(CH_2CH_2O)_n-$, p-

aminobenzyloxycarbonyl (PAB), Val-Cit-PAB, Val-Ala-PAB, Ala-Ala-Asn-PAB, Val-Ala, Asn-Ala, any amino acid except glycine, and combinations thereof; and

Y comprises an ALPP and/or ALPPL2 specific antigen binding molecule or recombinant fusion protein according to any of Claims 1 to 6, optionally in which the target-binding molecule-drug conjugate has a structure selected from:





; or

(iv) in which the toxin of the target-binding molecule-drug conjugate according to Claim 8 is Exatecan or an Exatecan derivative.

10. An antibody, antibody fragment or antigen-binding molecule that competes for binding to ALPP and/or ALPPL2 with a ALPP and/or ALPPL2-specific antigen binding molecule according to Claim 1 or 2.

11. An ALPP and/or ALPPL2 -specific chimeric antigen receptor (CAR) comprising at least one ALPP and/or ALPPL2 -specific antigen binding molecule according to Claim 1 or 2, fused or conjugated to at least one transmembrane region and at least one intracellular domain; or a cell comprising such a chimeric antigen receptor, in which the cell is preferably an engineered T-cell.

12. A nucleic acid sequence comprising a polynucleotide sequence that encodes a specific antigen binding molecule, recombinant fusion protein, recombinant fusion protein dimer or chimeric antigen receptor according to any preceding claim, a vector comprising such a nucleic acid sequence or a cell comprising such a vector.

13. A pharmaceutical composition comprising an ALPP and/or ALPPL2 specific antigen binding molecule according to Claim 1 or 2, a recombinant fusion protein according to Claim 3 or 4, a recombinant fusion protein dimer according to Claim 5 or 6, a CAR according to Claim 11, a cell according to Claim 11 or 12, a nucleic acid sequence according to Claim 12, a vector according to Claim 12, or a target-binding molecule-drug conjugate according to Claim 7, 8 or 9.

14. An ALPP and/or ALPPL2 specific antigen binding molecule according to Claim 1 or 2, a recombinant fusion protein according to Claim 3 or 4, a recombinant fusion protein dimer according to Claim 5 or 6, a CAR according to Claim 11, a cell according to Claim 11 or 12, a nucleic acid sequence according to Claim 12, a vector according to Claim 12, or a target-

binding molecule-drug conjugate according to Claim 7, 8 or 9 for use in therapy or for use in the treatment of cancer, optionally in which the cancer is an ALPP and/or ALPPL2-positive cancer type, optionally in which the cancer is selected from the group consisting of ovarian cancer, endometrial cancer, cervical cancer, gastric cancer, oesophageal cancer, bladder cancer, lung cancer, pancreatic cancer and testicular cancer.

15. Use of an ALPP and/or ALPPL2 specific antigen binding molecule according to Claim 1 or 2, a recombinant fusion protein according to Claim 3 or 4, a recombinant fusion protein dimer according to Claim 5 or 6, a CAR according to Claim 11, a cell according to Claim 11 or 12, a nucleic acid sequence according to Claim 12, a vector according to Claim 12, or a target-binding molecule-drug conjugate according to Claim 7, 8 or 9 in the manufacture of a medicament for the treatment of a disease in a patient in need thereof.

16. A method for preparing an ALPP and/or ALPPL2 specific antigen binding molecule according to Claim 1 or 2, a recombinant fusion protein according to Claim 3 or 4, a recombinant fusion protein dimer according to Claim 5 or 6, a CAR according to Claim 11, a cell according to Claim 11 or 12, a nucleic acid sequence according to Claim 12, a vector according to Claim 12, or a target-binding molecule-drug conjugate according to Claim 7, 8 or 9.