

CLAIMS

1. A receptor tyrosine kinase-like orphan receptor 1 (ROR1) specific antigen binding molecule comprising an amino acid sequence represented by the formula (I):

FW1-CDR1-FW2-HV2-FW3a-HV4-FW3b-CDR3-FW4 (I)

wherein

CDR3 is a CDR sequence having an amino acid sequence selected from the group consisting of YPWGAGAPYNVQWY (SEQ ID NO: 23), YPWGAGAPYLVQWY (SEQ ID NO: 20), YPWGAGAPWNVQWY (SEQ ID NO: 24), YPSGAGAPRPVQWY (SEQ ID NO: 11), YPWGAGAPCLVQWY (SEQ ID NO: 12), YPWGAGAPRLVQWY (SEQ ID NO: 13), YPWGAGAPRQVQWY (SEQ ID NO: 14), YPWGAGAPRSVQWY (SEQ ID NO: 15), YPWGAGAPSLVQWY (SEQ ID NO: 16), YPWGAGAPSNVQWY (SEQ ID NO: 17), YPWGAGAPSQVQWY (SEQ ID NO: 18), YPWGAGAPSSVQWY (SEQ ID NO: 19), YPWGAGAPWQVQWY (SEQ ID NO: 21), YPWGAGAPWSVQWY (SEQ ID NO: 22), and YPWGAGAPWLQWY (SEQ ID NO: 10);

CDR1 is a CDR sequence having an amino acid sequence selected from the group consisting of GANYGLAA (SEQ ID NO: 1), DANYGLAA (SEQ ID NO: 5), GANYDLA (SEQ ID NO: 2), GANYGLA (SEQ ID NO: 3), and GANYDLAA (SEQ ID NO: 4)

FW1 is a framework region;

FW2 is a framework region;

HV2 is a hypervariable sequence having an amino acid sequence selected from the group consisting of SSNQERISIS (SEQ ID NO: 6), and SSNKERISIS (SEQ ID NO: 7);

FW3a is a framework region;

HV4 is a hypervariable sequence having an amino acid sequence selected from the group consisting of NKRTM (SEQ ID NO: 8) and NKGTM (SEQ ID NO: 9);

FW3b is a framework region;

FW4 is a framework region;

wherein if CDR3 is YPWGAGAPWLVQWY (SEQ ID NO: 10) then CDR1 is selected from the group consisting of DANYGLAA (SEQ ID NO: 5), GANYGLSA (SEQ ID NO: 3) and GANYDLAA (SEQ ID NO: 4).

2. The ROR1-specific antigen binding molecule of claim 1 wherein:

CDR3 is a CDR sequence having an amino acid sequence selected from the group consisting of YPWGAGAPYINVQWY (SEQ ID NO: 23), YPWGAGAPYLVQWY (SEQ ID NO: 20) and YPWGAGAPWNVQWY (SEQ ID NO: 24), and/or

CDR1 is a CDR sequence having an amino acid sequence selected from the group consisting of GANYGLAA (SEQ ID NO: 1) and DANYGLAA (SEQ ID NO: 5).

3. The ROR1-specific antigen binding molecule of claim 1 or claim 2 wherein:

CDR3 is a CDR sequence having an amino acid sequence according to YPWGAGAPYINVQWY (SEQ ID NO: 23).

4. The ROR1-specific antigen binding molecule of any preceding claim wherein:

CDR3 is a CDR sequence having an amino acid sequence according to YPWGAGAPYINVQWY (SEQ ID NO: 23);

CDR1 is a CDR sequence having an amino acid sequence according to GANYGLAA (SEQ ID NO: 1);

HV2 is a hypervariable sequence having an amino acid sequence according to SSNQERISIS (SEQ ID NO: 6); and

HV4 is a hypervariable sequence having an amino acid sequence according to NKRTM (SEQ ID NO: 8).

5. The ROR1-specific antigen binding molecule of any one of claims 1 to 3 wherein:

CDR3 is a CDR sequence having an amino acid sequence according to YPWGAGAPYINVQWY (SEQ ID NO: 23);

CDR1 is a CDR sequence having an amino acid sequence according to DANYGLAA (SEQ ID NO: 5);

HV2 is a hypervariable sequence having an amino acid sequence according to SSNKERISIS (SEQ ID NO: 7); and

HV4 is a hypervariable sequence having an amino acid sequence according to NKGTM (SEQ ID NO: 9).

6. The ROR1-specific antigen binding molecule of any one of claims 1 to 3 wherein:

CDR3 is a CDR sequence having an amino acid sequence according to YPWGAGAPWLVQWY (SEQ ID NO: 10);

CDR1 is a CDR sequence having an amino acid sequence according to DANYGLAA (SEQ ID NO: 5);

HV2 is a hypervariable sequence having an amino acid sequence according to SSNKERISIS (SEQ ID NO: 7); and

HV4 is a hypervariable sequence having an amino acid sequence according to NKGTM (SEQ ID NO: 9).

7. A receptor tyrosine kinase-like orphan receptor 1 (ROR1) specific antigen binding molecule comprising an amino acid sequence represented by the formula (I):

FW1-CDR1-FW2-HV2-FW3a-HV4-FW3b-CDR3-FW4 (I)

wherein

CDR1 is a CDR sequence having an amino acid sequence selected from the group consisting of GTRYGLYS (SEQ ID NO: 25), GTRYGLYSS (SEQ ID NO: 26), DTRYALYS (SEQ ID NO: 27), DTRYALYSS (SEQ ID NO: 28), GTKYGLYA (SEQ ID NO: 29) and GTKYGLYAS (SEQ ID NO: 30);

FW1 is a framework region;

FW2 is a framework region;

HV2 is a hypervariable sequence having an amino acid sequence selected from the group consisting of SSDEERISIS (SEQ ID NO: 31), STDEERISIG (SEQ ID NO: 32), SPNKDRMIIG (SEQ ID NO: 33), and STDKERMIIG (SEQ ID NO: 34);

FW3a is a framework region;

HV4 is a hypervariable sequence having an amino acid sequence selected from the group consisting of NKGTK (SEQ ID NO: 35), NKGSK (SEQ ID NO: 36), NNGTK (SEQ ID NO: 37), and NNRSK (SEQ ID NO: 38);

FW3b is a framework region;

CDR3 is a CDR sequence having an amino acid sequence according to REARHPWLRQWY (SEQ ID NO: 39);

FW4 is a framework region.

8. The ROR1-specific antigen binding molecule of any preceding claim, wherein
- FW1 is a framework region of from 20 to 28 amino acids;
- FW2 is a framework region of from 6 to 14 amino acids;
- FW3a is a framework region of from 6 to 10 amino acids;
- FW3b is a framework region of from 17 to 24 amino acids; and/or
- FW4 is a framework region of from 7 to 14 amino acids.
9. The ROR1-specific antigen binding molecule of claim 8, wherein
- FW1 has an amino acid sequence selected from the group consisting of: ASVNQTPRTATKETGESLTINCVVT (SEQ ID NO: 40), TRVDQSPSSLSASVGDRVITITCVLT (SEQ ID NO: 41) and ASVTQSPRSASKETGESLTITCRVT (SEQ ID NO: 42), or a functional variant of any thereof with a sequence identity of at least 45%;
- FW2 has an amino acid sequence according to TYWYRKNPG (SEQ ID NO: 43), or a functional variant of any thereof with a sequence identity of at least 45%;
- FW3a has an amino acid sequence selected from the group consisting of: GRYVESV (SEQ ID NO: 44) and GRYSESV (SEQ ID NO: 45), or a functional variant of any thereof with a sequence identity of at least 45%;
- FW3b has an amino acid sequence selected from the group consisting of: SFSLRIKDLTVADSATYYCKA (SEQ ID NO: 84), SFTLTISLQPEDSATYYCRA (SEQ ID NO: 46) and SFSLRISSLTVEDSATYYCKA (SEQ ID NO: 47), or a functional variant of any thereof with a sequence identity of at least 45%;
- and/or
- FW4 has an amino acid sequence selected from the group consisting of: DGAGTVLTVN (SEQ ID NO: 48), DGAGTKVEIK (SEQ ID NO: 49) or DGQGTKLEVK (SEQ ID NO: 85) or a functional variant of any thereof with a sequence identity of at least 45%.
10. The ROR1-specific antigen binding molecule of claim 1, wherein the ROR1-specific antigen binding molecule comprises an amino acid sequence selected from the group consisting of: ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSLRIKDLTVADSATYYCKAYPWGAGAPYNVQWYDGAGTVLTVN (SEQ ID NO: 50); TRVDQSPSSLSASVGDRVITITCVLTDANYGLAATYWYRKNPGSSNKERISISGRYSESVNKGTMSTFTLTISLQPEDSATYYCRAYPWGAGAPWLQWYDGAGTKVEIK (SEQ ID NO: 51); ASVNQTPRTATKETGESLTINCVVTGANYDLSATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSLRIKDLTVADSATYYCKAYPSGAGAPRPVQWYDGAGTVLTVN (SEQ ID NO: 52); ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL

RIKDLTVADSATYYCKAYPWGAGAPCLVQWYDGAGTVLTVN (SEQ ID NO: 53);
ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL
RIKDLTVADSATYYCKAYPWGAGAPRLVQWYDGAGTVLTVN (SEQ ID NO: 54);
ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL
RIKDLTVADSATYYCKAYPWGAGAPRQVQWYDGAGTVLTVN (SEQ ID NO: 55);
ASVNQTPRTATKETGESLTINCVVTGANYGLSATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL
RIKDLTVADSATYYCKAYPWGAGAPRSVQWYDGAGTVLTVN (SEQ ID NO: 56);
ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL
RIKDLTVADSATYYCKAYPWGAGAPRSVQWYDGAGTVLTVN (SEQ ID NO: 57);
ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL
RIKDLTVADSATYYCKAYPWGAGAPSLVQWYDGAGTVLTVN (SEQ ID NO: 58);
ASVNQTPRTATKETGESLTINCVVTGANYGLSATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL
RIKDLTVADSATYYCKAYPWGAGAPSNVQWYDGAGTVLTVN (SEQ ID NO: 59);
ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL
RIKDLTVADSATYYCKAYPWGAGAPSQVQWYDGAGTVLTVN (SEQ ID NO: 60);
ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL
RIKDLTVADSATYYCKAYPWGAGAPSSVQWYDGAGTVLTVN (SEQ ID NO: 61);
ASVNQTPRTATKETGESLTINCVVTGANYGLSATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL
RIKDLTVADSATYYCKAYPWGAGAPWLQWYDGAGTVLTVN (SEQ ID NO: 62);
ASVNQTPRTATKETGESLTINCVVTGANYDLAATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL
RIKDLTVADSATYYCKAYPWGAGAPWLQWYDGAGTVLTVN (SEQ ID NO: 63);
ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL
RIKDLTVADSATYYCKAYPWGAGAPWNVQWYDGAGTVLTVN (SEQ ID NO: 64);
ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL
RIKDLTVADSATYYCKAYPWGAGAPWQVQWYDGAGTVLTVN (SEQ ID NO: 65);
ASVNQTPRTATKETGESLTINCVVTGANYGLSATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL
RIKDLTVADSATYYCKAYPWGAGAPWQVQWYDGAGTVLTVN (SEQ ID NO: 66);
ASVNQTPRTATKETGESLTINCVVTGANYDLAATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL
RIKDLTVADSATYYCKAYPWGAGAPWQVQWYDGAGTVLTVN (SEQ ID NO: 67);
ASVNQTPRTATKETGESLTINCVVTGANYDLAATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL
RIKDLTVADSATYYCKAYPWGAGAPWSVQWYDGAGTVLTVN (SEQ ID NO: 68);
ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL
RIKDLTVADSATYYCKAYPWGAGAPWSVQWYDGAGTVLTVN (SEQ ID NO: 69); and
ASVNQTPRTATKETGESLTINCVVTGANYGLSATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL
RIKDLTVADSATYYCKAYPWGAGAPWSVQWYDGAGTVLTVN (SEQ ID NO: 70);
or a functional variant having CDR1, HV2, HV4 and CDR2 sequences according to any thereof and
having FW1, FW2, FW3a, FW3b and FW4 sequences having a combined sequence identity of at least
45% to the combined FW1, FW2, FW3a, FW3b and FW4 sequences of any thereof.

11. The ROR1-specific antigen binding molecule of claim 1, wherein the ROR1-specific antigen binding molecule comprises an amino acid sequence according to
ASVNQTPRTATKETGESLTINC VVTGANYGLAATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL
RIKDLTVADSATYYCKAYPWGAGAPYNVQWYDGAGTVLTVN (SEQ ID NO: 50).

12. The ROR1-specific antigen binding molecule of claim 1, wherein the ROR1-specific antigen binding molecule comprises an amino acid sequence according to
TRVDQSPSSLSASVGDRVITITCVLTDANYGLAATYWYRKNPGSSNKERISISGRYSESVNKGTSFTL
TISSLQPEDSATYYCRAYPWGAGAPWLQWYDGAGTKVEIK (SEQ ID NO: 51).

13. The ROR1-specific antigen binding molecule of claim 1, wherein the ROR1-specific antigen binding molecule comprises an amino acid sequence selected from the group consisting of:
TRVDQSPSSLSASVGDRVITITCVLTDANYGLAATYWYRKNPGSSNKERISISGRYSESVNKGTSFTL
TISSLQPEDSATYYCRAYPWGAGAPYNVQWYDGAGTKVEIK (SEQ ID NO: 71);
ASVTQSPRSASKETGESLTITCRVTGANYGLAATYWYRKNPGSSNQERISISGRYSESVNKRTMSFSL
RISSLTVEDSATYYCKAYPWGAGAPYNVQWYDGQGTKLEVK (SEQ ID NO: 72);
TRVDQSPSSLSASVGDRVITITCVLTDANYGLAATYWYRKNPGSSNKERISISGRYSESVNKGTSFTL
TISSLQPEDSATYYCRAYPWGAGAPSSVQWYDGAGTKVEIK (SEQ ID NO: 73);
ASVTQSPRSASKETGESLTITCRVTGANYGLAATYWYRKNPGSSNQERISISGRYSESVNKRTMSFSL
RISSLTVEDSATYYCKAYPWGAGAPSSVQWYDGQGTKLEVK (SEQ ID NO: 74);
TRVDQSPSSLSASVGDRVITITCVLTDANYGLAATYWYRKNPGSSNKERISISGRYSESVNKGTSFTL
TISSLQPEDSATYYCRAYPWGAGAPRQVQWYDGAGTKVEIK (SEQ ID NO: 75); and
ASVTQSPRSASKETGESLTITCRVTGANYGLAATYWYRKNPGSSNQERISISGRYSESVNKRTMSFSL
RISSLTVEDSATYYCKAYPWGAGAPRQVQWYDGQGTKLEVK (SEQ ID NO: 76);
or a functional variant having CDR1, HV2, HV4 and CDR2 sequences according to any thereof and having FW1, FW2, FW3a, FW3b and FW4 sequences having a combined sequence identity of at least 45% to the combined FW1, FW2, FW3a, FW3b and FW4 sequences of any thereof.

14. The ROR1-specific antigen binding molecule of claim 1, wherein the ROR1-specific antigen binding molecule comprises an amino acid sequence according to
TRVDQSPSSLSASVGDRVITITCVLTDANYGLAATYWYRKNPGSSNKERISISGRYSESVNKGTSFTL
TISSLQPEDSATYYCRAYPWGAGAPYNVQWYDGAGTKVEIK (SEQ ID NO: 71).

15. The ROR1-specific antigen binding molecule of claim 7, wherein the ROR1-specific antigen binding molecule comprises an amino acid sequence selected from the group consisting of:
TRVDQSPSSLSASVGDRVITITCVLTGTRYGLYSTYWYRKNPGSSDEERISISGRYSESVNKGTKSFTL
TISSLQPEDSATYYCRAREARHPWLRQWYDGAGTKVEIK (SEQ ID NO: 77);
TRVDQSPSSLSASVGDRVITITCVLTGTRYGLYSSTYWYRKNPGSSDEERISISGRYSESVNKGTKSFTL
TISSLQPEDSATYYCRAREARHPWLRQWYDGAGTKVEIK (SEQ ID NO: 78);

TRVDQSPSSLSASVGDRVITITCVLTDTTRYALYSTYWYRKNPGSTDEERISIGGRYSESVNKGSKSFTL
TISSLQPEDSATYYCRAREARHPWLRQWYDGAGTKVEIK (SEQ ID NO: 79);
TRVDQSPSSLSASVGDRVITITCVLTDTTRYALYSSTYWYRKNPGSTDEERISIGGRYSESVNKGSKSFT
LTISSLQPEDSATYYCRAREARHPWLRQWYDGAGTKVEIK (SEQ ID NO: 80);
TRVDQSPSSLSASVGDRVITITCVLTGTTYGLYATYWYRKNPGSPNKDRMIIGGRYSESVNNGTKSFTL
TISSLQPEDSATYYCRAREARHPWLRQWYDGAGTKVEIK (SEQ ID NO: 81);
TRVDQSPSSLSASVGDRVITITCVLTGTTYGLYASTYWYRKNPGSPNKDRMIIGGRYSESVNNGTKSF
LTISSLQPEDSATYYCRAREARHPWLRQWYDGAGTKVEIK (SEQ ID NO: 82);
TRVDQSPSSLSASVGDRVITITCVLTGTTYGLYASTYWYRKNPGSTDKERIIGGRYSESVNNRKSFTL
TISSLQPEDSATYYCRAREARHPWLRQWYDGAGTKVEIK (SEQ ID NO: 83);

or a functional variant having CDR1, HV2, HV4 and CDR2 sequences according to any thereof and having FW1, FW2, FW3a, FW3b and FW4 sequences having a combined sequence identity of at least 45% to the combined FW1, FW2, FW3a, FW3b and FW4 sequences of any thereof.

16. The ROR1-specific antigen binding molecule of any preceding claim, wherein the ROR1-specific antigen binding molecule does not bind to receptor tyrosine kinase-like orphan receptor 2 (ROR2).
17. The ROR1-specific antigen binding molecule of any preceding claim, wherein the ROR1-specific antigen binding molecule binds to both human ROR1 and murine ROR1 (mROR1).
18. The ROR1-specific antigen binding molecule of any preceding claim, wherein the ROR1-specific antigen binding molecule binds to deglycosylated ROR1.
19. The ROR1-specific antigen binding molecule of any preceding claim, wherein the ROR1-specific antigen binding molecule is humanized.
20. The ROR1-specific antigen binding molecule of any one of claims 1 to 18, wherein the ROR1-specific antigen binding molecule is de-immunized.
21. The ROR1-specific antigen binding molecule of any one of claims 1 to 20, wherein the ROR1-specific antigen binding molecule is conjugated to a detectable label, dye, toxin, drug, pro-drug, radionuclide or biologically active molecule.
22. The ROR1-specific antigen binding molecule of any one of claims 1 to 21, wherein the specific antigen binding molecule selectively interacts with ROR1 protein with an affinity constant of approximately 0.01 to 50 nM, preferably 0.1 to 30 nM, even more preferably 0.1 to 10 nM.
23. The ROR1-specific antigen binding molecule of any one of claims 1 to 22, wherein the specific antigen binding molecule is capable of mediating killing of ROR1-expressing tumour cells.

24. The ROR1-specific antigen binding molecule of any one of claims 1 to 22, wherein the specific antigen binding molecule is capable of inhibiting cancer cell proliferation.
25. The ROR1-specific antigen binding molecule of any one of claims 1 to 22, wherein the specific antigen binding molecule is capable of being endocytosed upon binding to ROR1.
26. A recombinant fusion protein comprising a specific antigen binding molecule as claimed in any one of claims 1 to 25.
27. A recombinant fusion protein as claimed in claim 26, in which the specific antigen binding molecule is fused to one or more biologically active proteins.
28. A recombinant fusion protein as claimed in claim 27, wherein the specific antigen binding molecule is fused to one or more biologically active proteins via one or more linker domains.
29. The recombinant fusion protein as claimed in either claim 27 or 28, wherein at least one biologically active protein 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.
30. The recombinant fusion protein as claimed in claim 29, wherein the at least one biologically active protein is an immunoglobulin Fc region.
31. The recombinant fusion protein as claimed in claim 29, wherein the at least one biologically active protein is a fragment of an immunoglobulin Fc region selected from the group consisting of an Fc heavy chain, a CH2 region and a CH3 region.
32. The recombinant fusion protein as claimed in claim 31, wherein the fragment of an immunoglobulin Fc region is an Fc heavy chain, optionally wherein the Fc heavy chain is engineered to comprise one or more cysteine residues suitable for bioconjugation.
33. The recombinant fusion protein as claimed in any one of claims 31 to claim 32 wherein the fragment of an immunoglobulin Fc region is engineered to dimerize with a second fragment of an immunoglobulin Fc region.
34. The recombinant fusion protein as claimed in any one of claims 31 to 33 wherein the fragment of an immunoglobulin Fc region is engineered to dimerize with the second fragment of an

immunoglobulin Fc region by a method selected from the group consisting of knobs-into-holes (Y-T), knobs-into-holes (CW-CSAV), CH3 charge pairing, Fab-arm exchange, SEED technology, BEATtechnology, HA-TF, ZW1 approach, Biclonic approach, EW-RVT and Triomab.

35. The recombinant fusion protein as claimed in any one of claims 31 to claim 34 wherein one or more residues of the fragment of the immunoglobulin Fc region comprises one or more amino acid substitution suitable for heterodimerization with a second fragment of an immunoglobulin Fc region comprising one or more corresponding amino acid mutation.

36. The recombinant fusion protein as claimed in claim 35 wherein the one or more amino acid substitution is selected from the group consisting of T366Y, Y407T, S354C, T366W, Y349C, T366S, L368A and Y407V.

37. The recombinant fusion protein as claimed in claim 35 or claim 36 wherein the one or more amino acid substitution is selected from the group consisting of T366Y and Y407T.

38. A recombinant fusion protein comprising an antigen binding molecule comprising an amino acid sequence represented by the formula (I):

FW1-CDR1-FW2-HV2-FW3a-HV4-FW3b-CDR3-FW4 (I)

wherein

FW1 is a framework region

CDR1 is a CDR sequence

FW2 is a framework region

HV2 is a hypervariable sequence

FW3a is a framework region

HV4 is a hypervariable sequence

FW3b is a framework region

CDR3 is a CDR sequence

FW4 is a framework region

or a functional variant thereof,

wherein the antigen binding molecule is fused to a fragment of an immunoglobulin Fc region wherein the fragment of an immunoglobulin Fc region is engineered to dimerize with a second fragment of an immunoglobulin Fc region.

39. The recombinant fusion protein as claimed in claim 38, wherein the fragment of an immunoglobulin Fc region selected from the group consisting of an Fc heavy chain, a CH2 region and a CH3 region.

40. The recombinant fusion protein as claimed in claim 39, wherein the fragment of an immunoglobulin Fc region is an Fc heavy chain.

41. The recombinant fusion protein as claimed in any one of claims 38 to 40 wherein the fragment of an immunoglobulin Fc region is engineered to dimerize with the second fragment of an immunoglobulin Fc region by a method selected from the group consisting of knobs-into-holes (Y-T), knobs-into-holes (CW-CSAV), CH3 charge pairing, Fab-arm exchange, SEED technology, BEAT technology, HA-TF, ZW1 approach, Biclonic approach, EW-RVT and Triomab.

42. The recombinant fusion protein as claimed in any one of claims 38 to claim 41 wherein one or more residues of the fragment of the immunoglobulin Fc region comprises one or more amino acid substitution suitable for knobs-in-holes (KIH) dimerization with a second fragment of an immunoglobulin Fc region comprising one or more corresponding amino acid mutation.

43. The recombinant fusion protein as claimed in claim 42 wherein the one or more amino acid substitution is selected from the group consisting of T366Y, Y407T, S354C, T366W, Y349C, T366S, L368A and Y407V.

44. The recombinant fusion protein as claimed in claim 42 or claim 43 wherein the one or more amino acid substitution is selected from the group consisting of T366Y and Y407T.

45. The recombinant fusion protein as claimed in any one of claims 29 to 44 wherein the antigen binding molecule is a ROR1 specific antigen binding molecule.

46. The recombinant fusion protein as claimed in any one of claims 29 to 45 comprising a sequence according to SEQ ID NO: 146 or SEQ ID NO: 147.

47. The recombinant fusion protein as claimed in claim 38 comprising a sequence according to SEQ ID NO: 148.

48. A recombinant fusion protein dimer comprising
- (a) a first recombinant fusion protein, wherein the first recombinant fusion protein is a recombinant fusion protein as claimed in any one of claims 30 to 47, and
 - (b) a second recombinant fusion protein, wherein the second recombinant fusion protein comprises a second antigen binding molecule fused to a second fragment of an immunoglobulin Fc region engineered to dimerize with the first fragment of an immunoglobulin Fc region.
49. The recombinant fusion protein dimer as claimed in claim 48, wherein the second fragment of an immunoglobulin Fc region selected from the group consisting of an Fc heavy chain, a CH2 region and a CH3 region.
50. The recombinant fusion protein dimer as claimed in claim 49, wherein the second fragment of an immunoglobulin Fc region is an Fc heavy chain.
51. The recombinant fusion protein dimer as claimed in any one of claims 48 to 50 wherein the second fragment of an immunoglobulin Fc region is engineered to dimerize with the second fragment of an immunoglobulin Fc region by a method selected from the group consisting of knobs-into-holes (Y-T), knobs-into-holes (CW-CSAV), CH3 charge pairing, Fab-arm exchange, SEED technology, BEAT technology, HA-TF, ZW1 approach, Biclonic approach, EW-RVT and Triomab.
52. The recombinant fusion protein dimer as claimed in any one of claims 48 to claim 51 wherein one or more residues of the fragment of the immunoglobulin Fc region comprises one or more amino acid substitution suitable for knobs-in-holes (KIH) dimerization with a second fragment of an immunoglobulin Fc region comprising one or more corresponding amino acid mutation.
53. The recombinant fusion protein dimer as claimed in claim 52 wherein the one or more amino acid substitution is selected from the group consisting of T366Y, Y407T, S354C, T366W, Y349C, T366S, L368A and Y407V.
54. The recombinant fusion protein dimer as claimed in claim 52 or claim 53 wherein the one or more amino acid substitution is selected from the group consisting of T366Y and Y407T.
55. The recombinant fusion protein dimer as claimed in any one of claims 48 to 54 wherein the second antigen binding molecule is a ROR1 specific antigen binding molecule.
56. The recombinant fusion protein dimer according to any one of claims 48 to 55 wherein the second specific antigen binding molecule is an immunoglobulin, 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) or a VH domain.

57. The recombinant fusion protein dimer according to any one of claims 48 or 56 wherein
- (a) the first recombinant fusion protein comprises a sequence according to SEQ ID NO: 146 or SEQ ID NO: 147, and
 - (b) the second recombinant fusion protein comprises a sequence according to SEQ ID NO: 148.

58.. A ROR1-specific chimeric antigen receptor (CAR), comprising at least one ROR1-specific antigen binding molecule as defined in any one of claims 1 to 20, fused or conjugated to at least one transmembrane region and at least one intracellular domain.

59. A cell comprising a chimeric antigen receptor according to claim 58, which cell is preferably an engineered T-cell.

60. A nucleic acid sequence comprising a polynucleotide sequence that encodes a specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor according to any one of claims 1 to 58.

61. A vector comprising a nucleic acid sequence as claimed in claim 60, optionally further comprising one or more regulatory sequences.

62. A host cell comprising a vector as claimed in claim 61.

63. A method for preparing a specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor, comprising cultivating or maintaining a host cell comprising the polynucleotide of claim 60 under conditions such that said host cell produces the binding molecule, optionally further comprising isolating the binding molecule.

64.. A pharmaceutical composition comprising the specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor of any one of claims 1 to 58.

65.. The specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor of any one of claims 1 to 58, for use in therapy.

66.. The specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor of any one of claims 1 to 58, for use in the treatment of cancer.

67. The specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor of claim 66, wherein the cancer is a ROR1-positive cancer type.

68. The specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor of claim 66, wherein the cancer is selected from the group comprising blood cancers such as lymphomas and leukemias, chronic lymphocytic leukaemia (CLL), mantle cell lymphoma (MCL), B-cell acute lymphoblastic leukaemia (B-ALL), marginal zone lymphoma (MZL), non-Hodgkin lymphomas (NHL), acute myeloid leukemia (AML) and solid tumours including neuroblastoma, renal cancer, lung cancer, colon cancer, ovarian cancer, pancreatic cancer, breast cancer, skin cancer, uterine cancer, prostate cancer, thyroid cancer, Head and Neck cancer, bladder cancer, oesophageal cancer, stomach cancer or liver cancer.

69. The use of a specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor of any one of claims 1 to 58 in the manufacture of a medicament for the treatment of a disease in a patient in need thereof.

70. A method of treatment of a disease in a patient in need of treatment comprising administration to said patient of a therapeutically effective dosage of a specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor of any one of claims 1 to 58 or a pharmaceutical composition of claim 64.

71. The method of claim 70, wherein the disease is cancer.

72. The method of claim 71 wherein the cancer is a ROR1-positive cancer type.

73. The method of claim 71, wherein the cancer is selected from the group consisting of blood cancers such as lymphomas and leukaemias, chronic lymphocytic leukaemia (CLL), mantle cell lymphoma (MCL), B-cell acute lymphoblastic leukaemia (B-ALL), marginal zone lymphoma (MZL), non-Hodgkin lymphomas (NHL), acute myeloid leukemia (AML) and solid tumours including neuroblastoma, renal cancer, lung cancer, colon cancer, ovarian cancer, pancreatic cancer, breast cancer, skin cancer, uterine cancer, prostate cancer, thyroid cancer, Head and Neck cancer, bladder cancer, oesophageal cancer, stomach cancer or liver cancer.

74. A method of assaying for the presence of a target analyte in a sample, comprising the addition of a detectably labelled specific antigen binding molecule of any one of claims 1 to 25 or a recombinant fusion protein of claim 26 to 47, or a recombinant fusion protein dimer of any one of claims 48 to 57 to the sample and detecting the binding of the molecule to the target analyte.

75. A method of imaging a site of disease in a subject, comprising administration of a detectably labelled specific antigen binding molecule as claimed in any one of claims 1 to 25 or a detectably labelled recombinant fusion protein of any one of claim 26 to 47, or a detectably labelled recombinant fusion protein dimer of any one of claims 48 to 57 to a subject.

76. A method of diagnosis of a disease or medical condition in a subject comprising administration of a specific antigen binding molecule as claimed in any one of claims 1 to 25 or a recombinant fusion protein of claim 26 to 47, or a recombinant fusion protein dimer of any one of claims 48 to 57 .

77. An antibody, antibody fragment or antigen-binding molecule that competes for binding to ROR1 with the ROR1-specific antigen binding molecule of any one of claims 1 to 25.

78. A kit for diagnosing a subject suffering from cancer, or a pre-disposition thereto, or for providing a prognosis of the subject's condition, the kit comprising detection means for detecting the concentration of antigen present in a sample from a test subject, wherein the detection means comprises a ROR1-specific antigen binding molecule as defined in any one of claims 1 to 25, a recombinant fusion protein as defined in any one of claims 26 to 47, a recombinant fusion protein dimer as defined in any one of claims 48 to 57, a CAR as defined in claim 58, or a nucleic acid as defined in claim 60, each being optionally derivatized, wherein presence of antigen in the sample suggests that the subject suffers from cancer.

79. The kit according to claim 78, wherein the antigen comprises ROR1 protein, more preferably an extracellular domain thereof.

80. The kit according to claim 78, wherein the kit is used to identify the presence or absence of ROR1-positive cells in the sample, or determine the concentration thereof in the sample.

81. The kit according to claim 78, wherein the kit comprises a positive control and/or a negative control against which the assay is compared.

82. The kit according to claim 78, wherein the kit further comprises a label which may be detected.

83. A method for diagnosing a subject suffering from cancer, or a pre-disposition thereto, or for providing a prognosis of the subject's condition, the method comprising detecting the concentration of antigen present in a sample obtained from a subject, wherein the detection is achieved using a ROR1-specific antigen binding molecule as defined in any one of claims 1 to 25, a recombinant fusion protein as defined in any one of claims 26 to 47, a recombinant fusion protein dimer as defined in any one of claims 48 to 57, a CAR as defined in claim 58, or a nucleic acid sequence as defined in claim 60, each being optionally derivatized, and wherein presence of antigen in the sample suggests that the subject suffers from cancer.

84. A method of killing or inhibiting the growth of a cell expressing ROR1 in vitro or in a patient, which method comprises administering to the cell a pharmaceutically effective amount or dose of (i) ROR1-specific antigen binding molecule as defined in any one of claims 1 to 25, a recombinant fusion protein as defined in any one of claims 26 to 47, a recombinant fusion protein dimer as defined in any

one of claims 48 to 57, a nucleic acid as defined in claim 60, or the CAR or cell according to claim 58 or 59, or (ii) of a pharmaceutical composition according to claim 64.

85. The method of claim 84, wherein the cell expressing ROR1 is a cancer cell.

86. The method according to either claim 84 or 85, wherein the ROR1 is human ROR1.

87. A specific antigen binding molecule comprising an amino acid sequence represented by the formula (II):



wherein

FW1-CDR1-FW2-HV2-FW3a-HV4-FW3b-CDR3-FW4 is a ROR1-specific antigen binding molecule according to any one of claims 1 to 25

X and Y are optional amino acid sequences

wherein the specific antigen binding molecule is conjugated to a second moiety.

88. The specific antigen binding molecule of claim 87, wherein X or Y are individually either absent or selected from the group comprising an immunoglobulin, an immunoglobulin Fc 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.

89. The specific antigen binding molecule of either claim 87 or claim 88, wherein the conjugation is via a cysteine residue in the amino acid sequence of the specific antigen binding molecule.

90. The specific antigen binding molecule of any one of claims 87 to 89, wherein the second moiety is selected from the group comprising an immunoglobulin or antibody, an immunoglobulin Fc 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.

91. The specific antigen binding molecule of any one of claims 87 to 89, wherein the second moiety is selected from the group comprising detectable label, dye, toxin, drug, pro-drug, radionuclide or biologically active molecule.

92. The specific antigen binding molecule according to any one of claims 87 to 89 or 91, wherein the second moiety is at least one toxin selected from the group comprising:

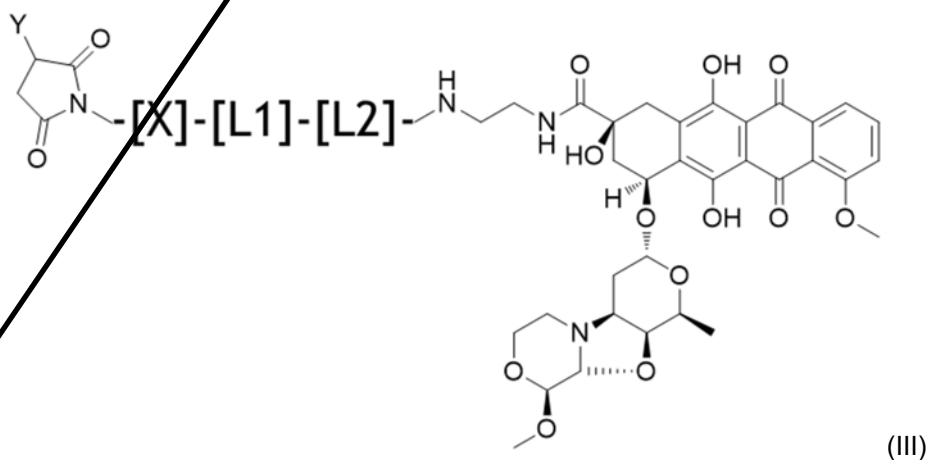
- maytansinoids,
- auristatins,
- anthracyclines, preferably PNU-derived anthracyclines
- amanitin derivatives, preferably α -amanitin derivatives
- calicheamicins,
- tubulysins
- duocarmycins
- radioisotopes - such as an alpha-emitting radionuclide, such as ^{227}Th or ^{225}Ac label
- liposomes comprising a toxic payload,
- protein toxins
- taxanes
- pyrrolbenzodiazepines and/or
- indolinobenzodiazepine pseudodimers and/or
- spliceosome inhibitors
- CDK11 inhibitors
- Pyridinobenzodiazepines
- Irinotecan and its derivatives

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

(a) a ROR1 specific antigen binding molecule according to any one of claims 1 to 25 or 87 to 90, or a recombinant fusion protein of any one of claims 26 to 47, or a recombinant fusion protein dimer of any one of claims 48 to 57, and

(b) an anthracycline (PNU) derivative,

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



wherein [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;

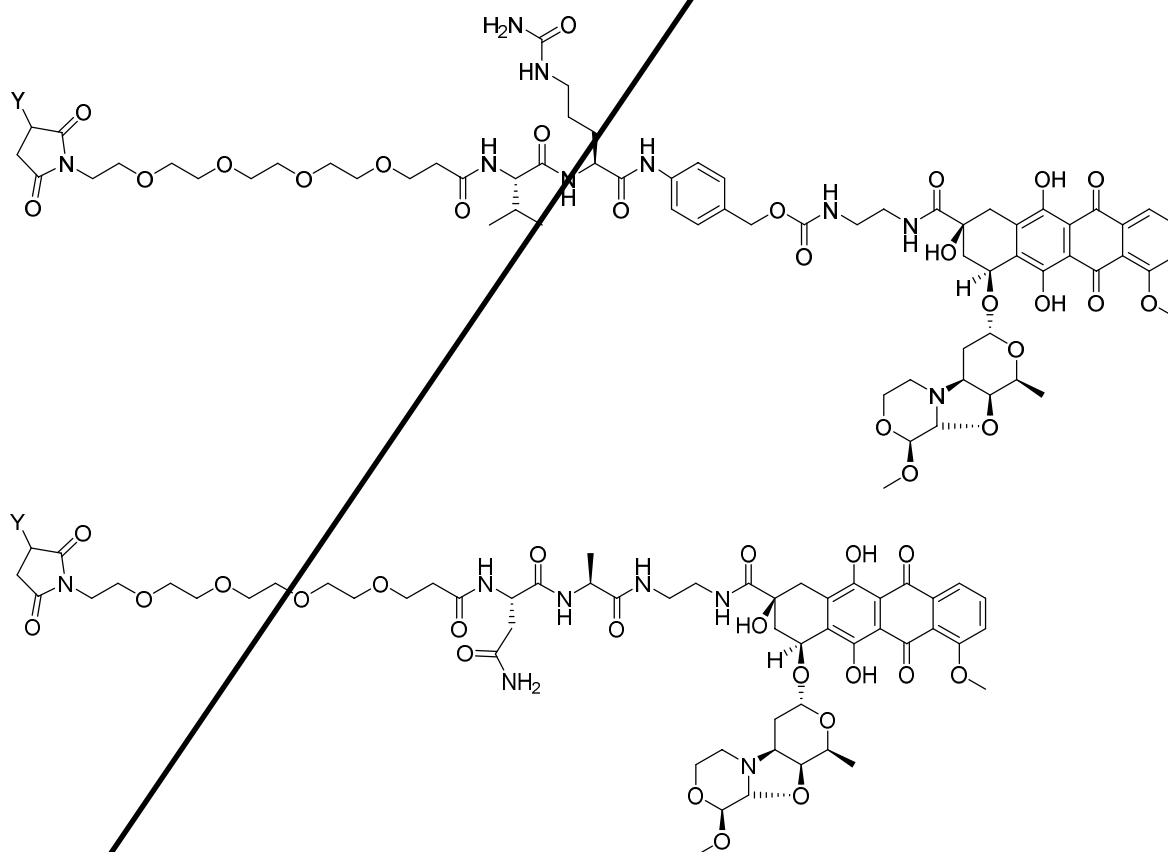
[L1] and [L2] are optional linkers selected from the group consisting of valine (Val), citrulline (Cit), alanine (Ala), asparagine (Asn), a peptide, $-(CH_2)_n-$, $-(CH_2CH_2O)_n-$, p-aminobenzyloxycarbonyl (PAB), Val-Cit-PAB, Val-Ala-PAB, Ala-Ala-Asn-PAB, Val-Ala, Asn-Ala, any amino acid except glycine, and combinations thereof; and

Y comprises a ROR1 specific antigen binding molecule according to any one of claims 1 to 25 or 87 to 90, or a recombinant fusion protein of any one of claims 26 to 47, or a recombinant fusion protein dimer of any one of claims 48 to 57.

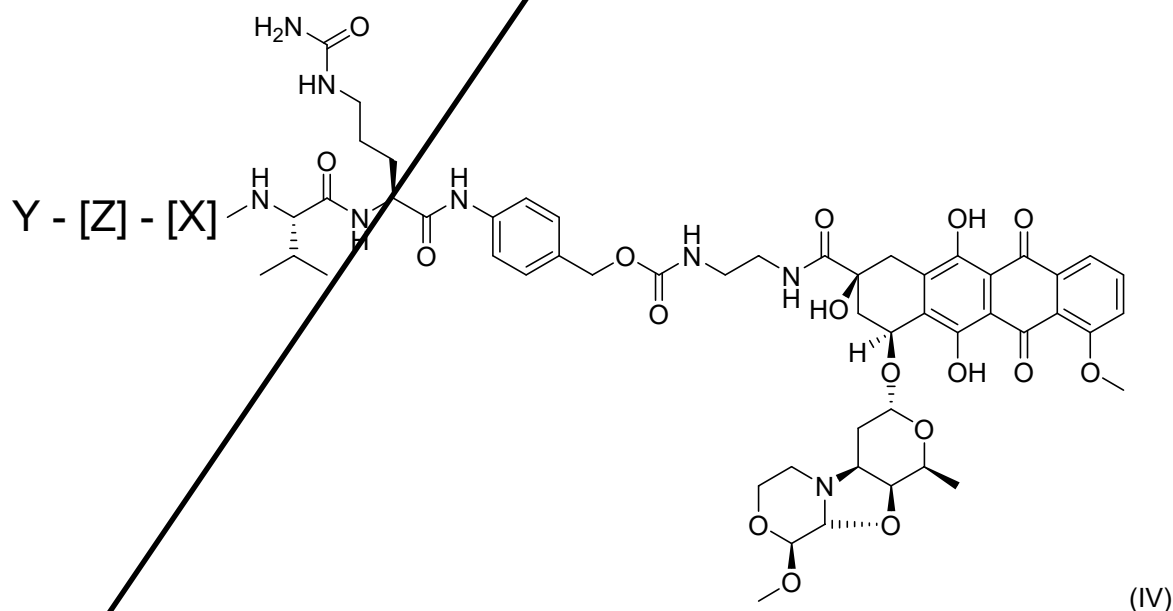
94. The target-binding molecule-drug conjugate of claim 93, wherein the target-binding molecule-drug conjugate of formula (III) comprises [L1], [L2] or [L1] and [L2].

95. The target-binding molecule-drug conjugate of any one of claims 93 to 94, wherein [L2] is p-aminobenzyloxycarbonyl (PAB) or alanine.

96. The target-binding molecule-drug conjugate of claim 93, wherein the target-binding molecule-drug conjugate has a structure selected from:



97. A target-binding molecule-drug conjugate, comprising
- (a) a ROR1 specific antigen binding molecule according to any one of claims 1 to 25 or 87 to 90, or a recombinant fusion protein of any one of claims 26 to 47, or a recombinant fusion protein dimer of any one of claims 48 to 57, and
- (b) an anthracycline (PNU) derivative,
- wherein the target-binding molecule-drug conjugate has the structure of formula (IV):



wherein [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;

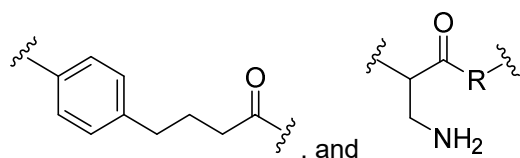
[Z] is a linker derived from a reactive group used to conjugate the anthracycline (PNU) derivative and the target-binding molecule; and

Y comprises a ROR1 specific antigen binding molecule according to any one of claims 1 to 25 or 87 to 90, or a recombinant fusion protein of any one of claims 26 to 47, or a recombinant fusion protein dimer of any one of claims 48 to 57.

98. The target-binding molecule-drug conjugate of claim 97, wherein [Z] is selected from the group consisting of a disulphide bond, an amide bond, an oxime bond, a hydrazone bond, a thioether bond, a 1, 2, 3 triazole and polyGly.

99. The target-binding molecule-drug conjugate of any one of claims 93 to 95 or 97 to 98, wherein

[X] is selected from the group comprising polyethylene glycol,



of the molecule and wherein [R] 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.

100. The target-binding molecule-drug conjugate of any one of claims 93 to 95 or 97 to 98, wherein [X] is polyethylene glycol.

101. The target-binding molecule-drug conjugate of any one of claims 93 to 100, wherein the target-binding molecule is a protein and the anthracycline (PNU) derivative is conjugated to a thiol-containing amino acid residue in the amino acid sequence of the protein or wherein the PNU derivative is conjugated via a thiol moiety incorporated by chemical modification at the N-terminus or C-terminus of the amino acid sequence of the protein.

102. The target-binding molecule-drug conjugate according to any one of claims 93 to 101, wherein Y comprises a ROR1 specific antigen binding molecule according to any one of claims 1 to 25 conjugated to the PNU derivative via a human immunoglobulin Fc region or fragment thereof.

103. The recombinant fusion protein of any one of claims 26 to 47 or any claim dependent thereon, or recombinant fusion protein dimer of any one of claims 48 to 57 or any claim dependent thereon, wherein the recombinant fusion protein comprises SEQ ID NO: 186 and/or SEQ ID NO: 187.

104. The recombinant fusion protein as claimed in any one of claims 29 to 45 or any claim dependent thereon, comprising a sequence according to any one or more of SEQ ID NO: 194, SEQ ID NO: 195, SEQ ID NO: 196, SEQ ID NO: 191, SEQ ID NO: 192, SEQ ID NO: 197, SEQ ID NO: 198, SEQ ID NO: 199, SEQ ID NO: 165, SEQ ID NO: 166, SEQ ID NO: 200, SEQ ID NO: 201, SEQ ID NO: 202, SEQ ID NO: 167, SEQ ID NO: 188, SEQ ID NO: 189, SEQ ID NO: 203, SEQ ID NO: 204, or SEQ ID NO: 205.

105. The specific antigen binding molecule of claim 89 or any claim dependent thereon, wherein the specific antigen binding molecule comprises SEQ ID NO: 178 and/or SEQ ID NO: 179.

106. The specific antigen binding molecule of claim 87 or any claim dependent thereon, wherein X or Y are individually either absent or selected from the group comprising 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.

107. The specific antigen binding molecule of claim 87 or any claim dependent thereon or claim 106, wherein X or Y are individually either absent or an immunoglobulin Fc region.

108. The specific antigen binding molecule of claim 106, wherein X or Y are individually either absent or a fragment of an immunoglobulin Fc region selected from the group consisting of an Fc heavy chain, a CH2 region and a CH3 region.

109. The specific antigen binding molecule of claim 108, wherein X or Y are individually either absent or a fragment of an immunoglobulin Fc region is an Fc heavy chain, optionally wherein the Fc heavy chain is engineered to comprise one or more cysteine residues suitable for bioconjugation.

110. The specific antigen binding molecule of claim 108 or 109, wherein X or Y are individually either absent or a fragment of an immunoglobulin Fc region engineered to dimerize with a second fragment of an immunoglobulin Fc region.

111. The specific antigen binding molecule of claim 108 to 110, wherein X or Y are individually either absent or a fragment of an immunoglobulin Fc region engineered to dimerize with the second fragment of an immunoglobulin Fc region by a method selected from the group consisting of knobs-into-holes (Y-T), knobs-into-holes (CW-CSAV), CH3 charge pairing, Fab-arm exchange, SEED technology, BEAT technology, HA-TF, ZW1 approach, Biclonic approach, EW-RVT and Triomab.

112. The specific antigen binding molecule of claim 108 to 111, wherein X or Y are individually either absent or a fragment of the immunoglobulin Fc region that comprises one or more amino acid

substitution suitable for heterodimerization with a second fragment of an immunoglobulin Fc region comprising one or more corresponding amino acid mutation.

113. The specific antigen binding molecule of claim 112 wherein the one or more amino acid substitution is selected from the group consisting of T366Y, Y407T, S354C, T366W, Y349C, T366S, L368A and Y407V.

114. The specific antigen binding molecule of claim 112 or claim 113 wherein the one or more amino acid substitution is selected from the group consisting of T366Y and Y407T.

CLAIMS

1. A receptor tyrosine kinase-like orphan receptor 1 (ROR1) specific antigen binding molecule comprising an amino acid sequence represented by the formula (I):

FW1-CDR1-FW2-HV2-FW3a-HV4-FW3b-CDR3-FW4 (I)

in which

CDR3 is a CDR sequence having an amino acid sequence selected from the group consisting of YPWGAGAPYINVQWY (SEQ ID NO: 23), YPWGAGAPYLVQWY (SEQ ID NO: 20), YPWGAGAPWNVQWY (SEQ ID NO: 24), YPSGAGAPRPVQWY (SEQ ID NO: 11), YPWGAGAPCLVQWY (SEQ ID NO: 12), YPWGAGAPRLVQWY (SEQ ID NO: 13), YPWGAGAPRQVQWY (SEQ ID NO: 14), YPWGAGAPRSVQWY (SEQ ID NO: 15), YPWGAGAPSLVQWY (SEQ ID NO: 16), YPWGAGAPSNVQWY (SEQ ID NO: 17), YPWGAGAPSQVQWY (SEQ ID NO: 18), YPWGAGAPSSVQWY (SEQ ID NO: 19), YPWGAGAPWQVQWY (SEQ ID NO: 21), YPWGAGAPWSVQWY (SEQ ID NO: 22), and YPWGAGAPWLQWY (SEQ ID NO: 10);

CDR1 is a CDR sequence having an amino acid sequence selected from the group consisting of GANYGLAA (SEQ ID NO: 1), DANYGLAA (SEQ ID NO: 5), GANYDLA (SEQ ID NO: 2), GANYGLA (SEQ ID NO: 3), and GANYDLA (SEQ ID NO: 4)

FW1 is a framework region;

FW2 is a framework region;

HV2 is a hypervariable sequence having an amino acid sequence selected from the group consisting of SSNQERIS (SEQ ID NO: 6), and SSNKERIS (SEQ ID NO: 7);

FW3a is a framework region;

HV4 is a hypervariable sequence having an amino acid sequence selected from the group consisting of NKRTM (SEQ ID NO: 8) and NKGTM (SEQ ID NO: 9);

FW3b is a framework region;

FW4 is a framework region;

in which if CDR3 is YPWGAGAPWLQWY (SEQ ID NO: 10) then CDR1 is selected from the group consisting of DANYGLAA (SEQ ID NO: 5), GANYGLSA (SEQ ID NO: 3) and GANYDLAA (SEQ ID NO: 4).

2. An ROR1-specific antigen binding molecule according to Claim 1, in which

FW1 is a framework region of from 20 to 28 amino acids;

FW2 is a framework region of from 6 to 14 amino acids;

FW3a is a framework region of from 6 to 10 amino acids;

FW3b is a framework region of from 17 to 24 amino acids; and/or

FW4 is a framework region of from 7 to 14 amino acids.

3. An ROR1-specific antigen binding molecule according to Claim 2, in which

FW1 has an amino acid sequence selected from the group consisting of:

ASVNQTPRTATKETGESLTINCVVT (SEQ ID NO: 40),

TRVDQSPSSLSASVGDRVTITCVLT (SEQ ID NO: 41) and

ASVTQSPRSASKETGESLTITCRVT (SEQ ID NO: 42) or a functional variant of any thereof with a sequence identity of at least 45%;

FW2 has an amino acid sequence according to TYWYRKNPG (SEQ ID NO: 43) or a functional variant thereof with a sequence identity of at least 45%;

FW3a has an amino acid sequence selected from the group consisting of: GRYVESV (SEQ ID NO: 44) and GRYSESV (SEQ ID NO: 45) or a functional variant of any thereof with a sequence identity of at least 45%;

FW3b has an amino acid sequence selected from the group consisting of:

SFSLRIKDLTVADSATYYCKA (SEQ ID NO: 84), SFTLTISLQPEDSATYYCRA

(SEQ ID NO: 46) and SFSLRISSLTVEDSATYYCKA (SEQ ID NO: 47) or a functional variant of any thereof with a sequence identity of at least 45%;

and/or

FW4 has an amino acid sequence selected from the group consisting of:

DGAGTVLTVN (SEQ ID NO: 48), DGAGTKVEIK (SEQ ID NO: 49) or

DGQGTKLEVK (SEQ ID NO: 85) or a functional variant of any thereof with a sequence identity of at least 45%.

4. An ROR1-specific antigen binding molecule according to Claim 1, in which the ROR1-specific antigen binding molecule comprises an amino acid sequence selected from the group consisting of:

(a)

ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISI
SGRYVESVNKRTMSFSLRIKDLTVADSATYYCKAYPWGAGAPYNVQWYDGAG
TVLTVN (SEQ ID NO: 50);

(b)

TRVDQSPSSLSASVGDRVTITCVLTDANYGLAATYWYRKNPGSSNKERISIS
GRYSESVNKGTMSTLTISLQPEDSATYYCRAYPWGAGAPWLQWYDGAGTK
VEIK (SEQ ID NO: 51);

(c)

ASVNQTPRTATKETGESLTINCVVTGANYDLSATYWYRKNPGSSNQERISIS
GRYVESVNKRTMSFSLRIKDLTVADSATYYCKAYPSGAGAPRPVQWYDGAGTV
LTVN (SEQ ID NO: 52);

(d)

ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISI
SGRYVESVNKRTMSFSLRIKDLTVADSATYYCKAYPWGAGAPCLVQWYDGAGT
VLTVN (SEQ ID NO: 53);

(e)

ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISI
SGRYVESVNKRTMSFSLRIKDLTVADSATYYCKAYPWGAGAPRLVQWYDGAGT
VLTVN (SEQ ID NO: 54);

(f)

ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISI
SGRYVESVNKRTMSFSLRIKDLTVADSATYYCKAYPWGAGAPRQVQWYDGAG
TVLTVN (SEQ ID NO: 55);

(g)

ASVNQTPRTATKETGESLTINCVVTGANYGLSATYWYRKNPGSSNQERISIS
GRYVESVKNKRTMSFSLRIKDLTVADSATYYCKAYPWGAGAPRSVQWYDGAGT
VLTVN (SEQ ID NO: 56);

(h)

ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISI
SGRYVESVKNKRTMSFSLRIKDLTVADSATYYCKAYPWGAGAPRSVQWYDGAGT
VLTVN (SEQ ID NO: 57);

(i)

ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISI
SGRYVESVKNKRTMSFSLRIKDLTVADSATYYCKAYPWGAGAPSLVQWYDGAGT
VLTVN (SEQ ID NO: 58);

(j)

ASVNQTPRTATKETGESLTINCVVTGANYGLSATYWYRKNPGSSNQERISIS
GRYVESVKNKRTMSFSLRIKDLTVADSATYYCKAYPWGAGAPSNVQWYDGAGT
VLTVN (SEQ ID NO: 59);

(k)

ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISI
SGRYVESVKNKRTMSFSLRIKDLTVADSATYYCKAYPWGAGAPSQVQWYDGAGT
VLTVN (SEQ ID NO: 60);

(l)

ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISI
SGRYVESVKNKRTMSFSLRIKDLTVADSATYYCKAYPWGAGAPSSVQWYDGAGT
VLTVN (SEQ ID NO: 61);

(m)

ASVNQTPRTATKETGESLTINCVVTGANYGLSATYWYRKNPGSSNQERISIS
GRYVESVKNKRTMSFSLRIKDLTVADSATYYCKAYPWGAGAPWLQWYDGAGT
VLTVN (SEQ ID NO: 62);

(n)

ASVNQTPRTATKETGESLTINCVVTGANYDLAATYWYRKNPGSSNQERISI

SGRYVESVNKRTMSFSLRIKDLTVADSATYYCKAYPWGAGAPWLVQWYDGAG
TVLTVN (SEQ ID NO: 63);

(o)

ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISI
SGRYVESVNKRTMSFSLRIKDLTVADSATYYCKAYPWGAGAPWNVQWYDGAG
TVLTVN (SEQ ID NO: 64);

(p)

ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISI
SGRYVESVNKRTMSFSLRIKDLTVADSATYYCKAYPWGAGAPWQVQWYDGAG
TVLTVN (SEQ ID NO: 65);

(q)

ASVNQTPRTATKETGESLTINCVVTGANYGLSATYWYRKNPGSSNQERISIS
GRYVESVNKRTMSFSLRIKDLTVADSATYYCKAYPWGAGAPWQVQWYDGAGT
VLTVN (SEQ ID NO: 66);

(r)

ASVNQTPRTATKETGESLTINCVVTGANYDLAATYWYRKNPGSSNQERISI
SGRYVESVNKRTMSFSLRIKDLTVADSATYYCKAYPWGAGAPWQVQWYDGAG
TVLTVN (SEQ ID NO: 67);

(s)

ASVNQTPRTATKETGESLTINCVVTGANYDLAATYWYRKNPGSSNQERISI
SGRYVESVNKRTMSFSLRIKDLTVADSATYYCKAYPWGAGAPWSVQWYDGAG
TVLTVN (SEQ ID NO: 68);

(t)

ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISI
SGRYVESVNKRTMSFSLRIKDLTVADSATYYCKAYPWGAGAPWSVQWYDGAG
TVLTVN (SEQ ID NO: 69); and

(u)

ASVNQTPRTATKETGESLTINCVVTGANYGLSATYWYRKNPGSSNQERISIS
GRYVESVNKRTMSFSLRIKDLTVADSATYYCKAYPWGAGAPWSVQWYDGAGT
VLTVN (SEQ ID NO: 70);

(v)

TRVDQSPSSLASVGDRVTITCVLTDANYGLAATYWYRKNPGSSNKERISIS
GRYSESVNKGTMSTFTLTISLQPEDSATYYCRAYPWGAGAPYNVQWYDGAGTK
VEIK (SEQ ID NO: 71);

(w)

ASVTQSPRSASKETGESLTITCRVTGANYGLAATYWYRKNPGSSNQERISIS
GRYSESVNKRTMSFSLRISSLTVEDSATYYCKAYPWGAGAPYNVQWYDGQGTK
LEVK (SEQ ID NO: 72);

(x)

TRVDQSPSSLASVGDRVTITCVLTDANYGLAATYWYRKNPGSSNKERISIS
GRYSESVNKGTMSTFTLTISLQPEDSATYYCRAYPWGAGAPSSVQWYDGAGTK
VEIK (SEQ ID NO: 73);

(y)

ASVTQSPRSASKETGESLTITCRVTGANYGLAATYWYRKNPGSSNQERISIS
GRYSESVNKRTMSFSLRISSLTVEDSATYYCKAYPWGAGAPSSVQWYDGQGTK
LEVK (SEQ ID NO: 74);

(z)

TRVDQSPSSLASVGDRVTITCVLTDANYGLAATYWYRKNPGSSNKERISIS
GRYSESVNKGTMSTFTLTISLQPEDSATYYCRAYPWGAGAPRQVQWYDGAGTK
VEIK (SEQ ID NO: 75); and

(aa)

ASVTQSPRSASKETGESLTITCRVTGANYGLAATYWYRKNPGSSNQERISIS
GRYSESVNKRTMSFSLRISSLTVEDSATYYCKAYPWGAGAPRQVQWYDGQGTK
LEVK (SEQ ID NO: 76);

or a functional variant having CDR1, HV2, HV4 and CDR2 sequences according to any thereof and having FW1, FW2, FW3a, FW3b and FW4 sequences having a combined sequence identity of at least 45% to the combined FW1, FW2, FW3a, FW3b and FW4 sequences of any thereof.

5. An ROR1-specific antigen binding molecule according to any preceding claim, in which the ROR1-specific antigen binding molecule:

- (a) does not bind to receptor tyrosine kinase-like orphan receptor 2 (ROR2);
 - (b) binds to both human ROR1 and murine ROR1 (mROR1);
 - (c) binds to deglycosylated ROR1;
 - (d) is humanized;
 - (e) is de-immunized.
6. An ROR1-specific antigen binding molecule according to any preceding claim, in which the ROR1-specific antigen binding molecule is conjugated to a detectable label, dye, toxin, drug, pro-drug, radionuclide or biologically active molecule.
7. An ROR1-specific antigen binding molecule according to any preceding claim, in which the specific antigen binding molecule:
- (a) selectively interacts with ROR1 protein with an affinity constant of approximately 0.01 to 50 nM, preferably 0.1 to 30 nM, even more preferably 0.1 to 10 nM;
 - (b) is capable of mediating killing of ROR1-expressing tumour cells;
 - (c) is capable of inhibiting cancer cell proliferation; and/or
 - (d) is capable of being endocytosed upon binding to ROR1.
8. A recombinant fusion protein comprising an ROR1-specific antigen binding molecule according to any preceding claim.
9. A recombinant fusion protein according to Claim 8, in which the ROR1-specific antigen binding molecule is fused to one or more biologically active proteins, optionally in which:
- (a) the specific antigen binding molecule is fused to one or more biologically active proteins via one or more linker domains; and/or
 - (b) the at least one biologically active protein 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, optionally in which the Fc heavy chain is engineered to comprise one or more cysteine residues suitable for bioconjugation.

10. A recombinant fusion protein according to Claim 9, in which the fragment of an immunoglobulin Fc region is engineered to dimerize with a second fragment of an immunoglobulin Fc region, optionally in which:

- (a) one or more residues of the fragment of the immunoglobulin Fc region comprises one or more amino acid substitution suitable for heterodimerization with a second fragment of an immunoglobulin Fc region comprising one or more corresponding amino acid mutation; and/or
- (b) the fragment of an immunoglobulin Fc region is engineered to dimerize with the second fragment of an immunoglobulin Fc region by a method selected from the group consisting of knobs-into-holes (Y-T), knobs-into-holes (CW-CSAV), CH3 charge pairing, Fab-arm exchange, SEED technology, BEAT technology, HA-TF, ZW1 approach, Biclonic approach, EW-RVT and Triomab, further optionally in which the one or more amino acid substitution is selected from the group consisting of T366Y, Y407T, S354C, T366W, Y349C, T366S, L368A and Y407V.

11. A recombinant fusion protein according to Claim 8, 9 or 10, comprising a sequence according to SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, SEQ ID NO: 186, SEQ ID NO: 187, SEQ ID NO: 194, SEQ ID NO: 195, SEQ ID NO: 196, SEQ ID NO: 191, SEQ ID NO: 192, SEQ ID NO: 197, SEQ ID NO: 198, SEQ ID NO: 199, SEQ ID NO: 165, SEQ ID NO: 166, SEQ ID NO: 200, SEQ ID NO: 201, SEQ ID NO: 202, SEQ ID NO: 167, SEQ ID NO: 188, SEQ ID NO: 189, SEQ ID NO: 203, SEQ ID NO: 204 or SEQ ID NO: 205.

12. A recombinant fusion protein dimer comprising:

- (a) a first recombinant fusion protein, in which the first recombinant fusion protein is a recombinant fusion protein according to any of Claims 8 to 11, and
- (b) a second recombinant fusion protein, in which the second recombinant fusion protein comprises a second antigen binding molecule fused to a second fragment of an immunoglobulin Fc region engineered to dimerize with the first fragment of an immunoglobulin Fc region.

13. A recombinant fusion protein dimer according to Claim 12, in which:

- (a) the second fragment of an immunoglobulin Fc region is selected from the group consisting of an Fc heavy chain, a CH2 region and a CH3 region;
 - (b) the second fragment of an immunoglobulin Fc region is engineered to dimerize with the second fragment of an immunoglobulin Fc region by a method selected from the group consisting of knobs-into-holes (Y-T), knobs-into-holes (CW-CSAV), CH3 charge pairing, Fab-arm exchange, SEED technology, BEAT technology, HA-TF, ZW1 approach, Biclonic approach, EW-RVT and Triomab;
 - (c) one or more residues of the fragment of the immunoglobulin Fc region comprises one or more amino acid substitution suitable for knobs-in-holes (KIH) dimerization with a second fragment of an immunoglobulin Fc region comprising one or more corresponding amino acid mutation, optionally in which the one or more amino acid substitution is selected from the group consisting of T366Y, Y407T, S354C, T366W, Y349C, T366S, L368A and Y407V;
 - (d) the second antigen binding molecule is an ROR1 specific antigen binding molecule;
 - (e) the second specific antigen binding molecule is an immunoglobulin, 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) or a VH domain;
 - (f) the first recombinant fusion protein comprises a sequence according to SEQ ID NO: 146 or SEQ ID NO: 147, and/or the second recombinant fusion protein comprises a sequence according to SEQ ID NO: 148.
14. An ROR1-specific chimeric antigen receptor (CAR) comprising at least one ROR1-specific antigen binding molecule as defined in any of Claims 1 to 7, fused or conjugated to at least one transmembrane region and at least one intracellular domain.
15. A cell comprising a chimeric antigen receptor according to Claim 14, which cell is preferably an engineered T-cell.
16. A nucleic acid sequence comprising a polynucleotide sequence that encodes a specific antigen binding molecule according to any of Claims 1 to 7, a recombinant fusion protein

according to any of Claims 8 to 11, a recombinant fusion protein dimer according to Claim 12 or 13 or a chimeric antigen receptor according to Claim 14.

17. A vector comprising a nucleic acid sequence according to Claim 16, optionally further comprising one or more regulatory sequences.

18. A host cell comprising a vector according to Claim 17.

19. A method for preparing a specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor, comprising cultivating or maintaining a host cell comprising a polynucleotide according to Claim 16 under conditions such that the host cell produces the binding molecule, optionally further comprising isolating the binding molecule.

20. A pharmaceutical composition comprising a specific antigen binding molecule according to any of Claims 1 to 7, a recombinant fusion protein according to any of Claims 8 to 11, a recombinant fusion protein dimer according to Claim 12 or 13 or a chimeric antigen receptor according to Claim 14.

21. A specific antigen binding molecule according to any of Claims 1 to 7, a recombinant fusion protein according to any of Claims 8 to 11, a recombinant fusion protein dimer according to Claim 12 or 13, a chimeric antigen receptor according to Claim 14 or a pharmaceutical composition according to Claim 20, for use in the treatment of cancer.

22. A specific antigen binding molecule according to any of Claims 1 to 7, a recombinant fusion protein according to any of Claims 8 to 11, a recombinant fusion protein dimer according to Claim 12 or 13, a chimeric antigen receptor according to Claim 14 or a pharmaceutical composition according to Claim 20, for use in a method of treatment of cancer in a patient in need of treatment, in which a therapeutically effective dosage of the specific antigen binding molecule, recombinant fusion protein, chimeric antigen receptor or pharmaceutical composition is to be administered to the patient.

23. A specific antigen binding molecule, recombinant fusion protein, recombinant fusion protein dimer, chimeric antigen receptor or composition for use according to Claim 22, in which the cancer is an ROR1-positive cancer type, optionally in which the cancer is selected from the group consisting of blood cancers such as lymphomas and leukaemias, chronic lymphocytic leukaemia (CLL), mantle cell lymphoma (MCL), B-cell acute lymphoblastic

leukaemia (B-ALL), marginal zone lymphoma (MZL), non-Hodgkin lymphomas (NHL), acute myeloid leukemia (AML) and solid tumours including neuroblastoma, renal cancer, lung cancer, colon cancer, ovarian cancer, pancreatic cancer, breast cancer, skin cancer, uterine cancer, prostate cancer, thyroid cancer, Head and Neck cancer, bladder cancer, oesophageal cancer, stomach cancer or liver cancer.

24. A method of assaying for the presence of a target analyte in a sample, comprising the addition of a detectably labelled specific antigen binding molecule according to any of Claims 1 to 7, a recombinant fusion protein according to any of Claims 8 to 11 or a recombinant fusion protein dimer according to Claim 12 or 13 to the sample and detecting the binding of the molecule to the target analyte.

25. A method of imaging a site of disease in a subject, in which a detectably labelled specific antigen binding molecule according to any of Claims 1 to 7, a detectably labelled recombinant fusion protein according to any of Claims 8 to 11 or a detectably labelled recombinant fusion protein dimer according to Claim 12 or 13 is to be administered to a subject.

26. An antibody, antibody fragment or antigen-binding molecule that competes for binding to ROR1 with the ROR1-specific antigen binding molecule according to any of Claims 1 to 7.

27. A kit for diagnosing a subject suffering from cancer or a pre-disposition thereto or for providing a prognosis of the subject's condition, the kit comprising detection means for detecting the concentration of antigen present in a sample from a test subject, in which the detection means comprises an ROR1-specific antigen binding molecule according to any of Claims 1 to 7, a recombinant fusion protein according to any of Claims 8 to 11, a recombinant fusion protein dimer according to Claim 12 or 13, a CAR according to Claim 14 or a nucleic acid according to Claim 16, each being optionally derivatized, in which the presence of antigen in the sample suggests that the subject suffers from cancer, optionally in which:

- (a) the antigen comprises ROR1 protein, more preferably an extracellular domain thereof;
- (b) the kit is used to identify the presence or absence of ROR1-positive cells in the sample or determine the concentration thereof in the sample;

(c) the kit comprises a positive control and/or a negative control against which the assay is compared; and/or

(d) the kit further comprises a label which may be detected.

28. A method for diagnosing a subject suffering from cancer or a pre-disposition thereto or for providing a prognosis of the subject's condition, the method comprising detecting the concentration of antigen present in a sample obtained from a subject, in which the detection is achieved using an ROR1-specific antigen binding molecule according to any of Claims 1 to 7, a recombinant fusion protein according to any of Claims 8 to 11, a recombinant fusion protein dimer according to Claim 12 or 13, a CAR according to Claim 14 or a nucleic acid sequence according to Claim 16, each being optionally derivatized, and in which presence of antigen in the sample suggests that the subject suffers from cancer.

29. A method of killing or inhibiting the growth of a cell expressing ROR1 *in vitro*, which method comprises administering to the cell a pharmaceutically effective amount or dose of (i) an ROR1-specific antigen binding molecule according to any of Claims 1 to 7, a recombinant fusion protein according to any of Claims 8 to 11, a recombinant fusion protein dimer according to Claim 12 or 13, a nucleic acid according to Claim 16 or a CAR or cell according to Claim 14 or (ii) a pharmaceutical composition according to Claim 20, optionally in which the cell expressing ROR1 is a cancer cell, and further optionally in which the ROR1 is human ROR1.

30. A specific antigen binding molecule according to any of Claims 1 to 7, in which the binding molecule comprises an amino acid sequence represented by the formula (II):



in which

FW1-CDR1-FW2-HV2-FW3a-HV4-FW3b-CDR3-FW4 is an ROR1-specific antigen binding molecule according to any of Claims 1 to 7

X and Y are optional amino acid sequences

in which the specific antigen binding molecule is conjugated to a second moiety, optionally in which:

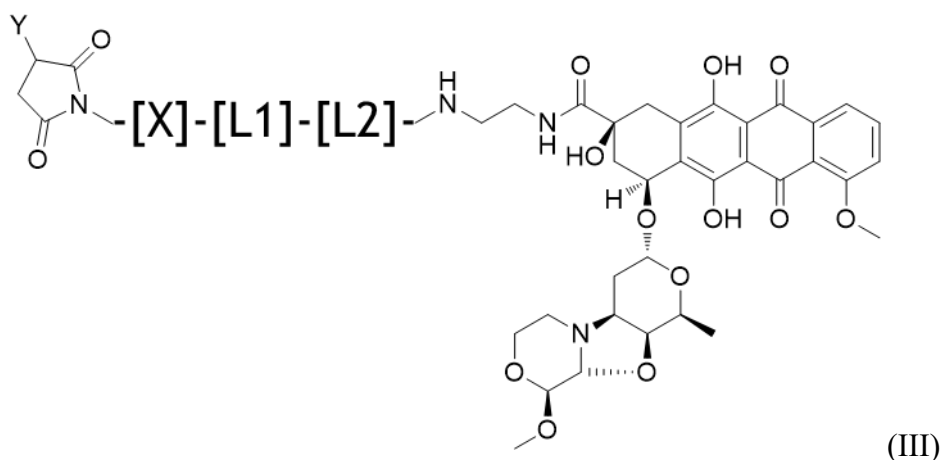
- (a) X or Y are individually either absent or selected from the group comprising an immunoglobulin, an immunoglobulin Fc region, an immunoglobulin Fab region, a Fab', a Fv, a Fv-Fc, a single chain Fv (scFv), scFv-Fc, (scFv)₂, a diabody, a triabody, a tetrabody, a bispecific t-cell engager, an intein, a VNAR domain, a single domain antibody (sdAb), a VH domain or a scaffold protein;
- (b) the conjugation is via a cysteine residue in the amino acid sequence of the specific antigen binding molecule; and/or
- (c) the second moiety is selected from:
 - (i) the group comprising an immunoglobulin or antibody, an immunoglobulin Fc 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; or
 - (ii) the group comprising detectable label, dye, toxin, drug, pro-drug, radionuclide or biologically active molecule, optionally in which toxin is selected from the group comprising:
 - maytansinoids,
 - auristatins,
 - anthracyclines, preferably PNU-derived anthracyclines,
 - amanitin derivatives, preferably α -amanitin derivatives,
 - calicheamicins,
 - tubulysins,
 - duocarmycins,
 - radioisotopes - such as an alpha-emitting radionuclide, such as ²²⁷Th or ²²⁵Ac label,
 - liposomes comprising a toxic payload,
 - protein toxins,
 - taxanes,

pyrrolbenzodiazepines and/or
 indolinobenzodiazepine pseudodimers and/or
 spliceosome inhibitors,
 CDK11 inhibitors,
 pyridinobenzodiazepines,
 Irinotecan and its derivatives.

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

- (a) an ROR1 specific antigen binding molecule according to any of Claims 1 to 7, a recombinant fusion protein according to any of Claims 8 to 11 or a recombinant fusion protein dimer according to Claim 12 or 13, and
- (b) an anthracycline (PNU) derivative,

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

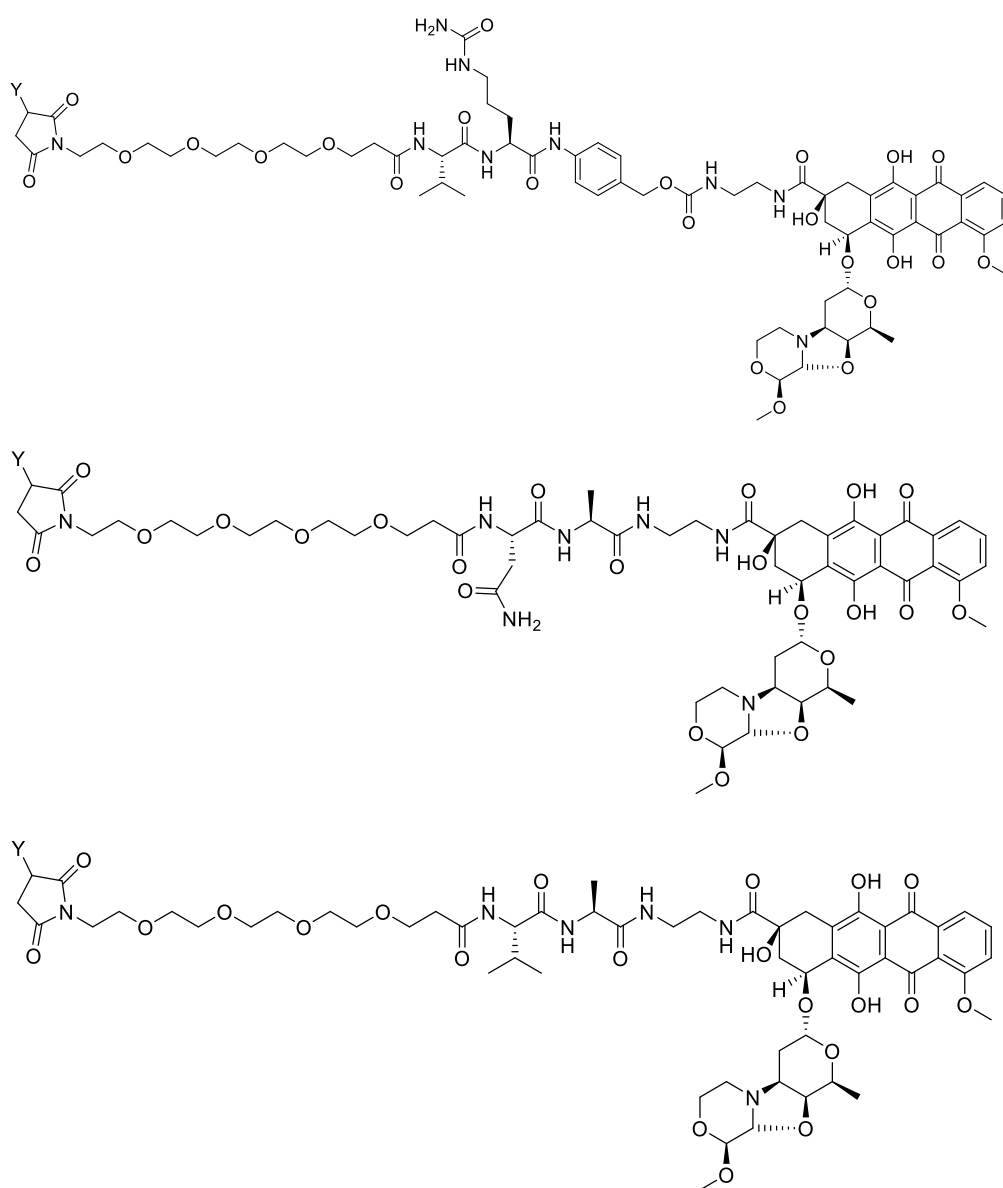


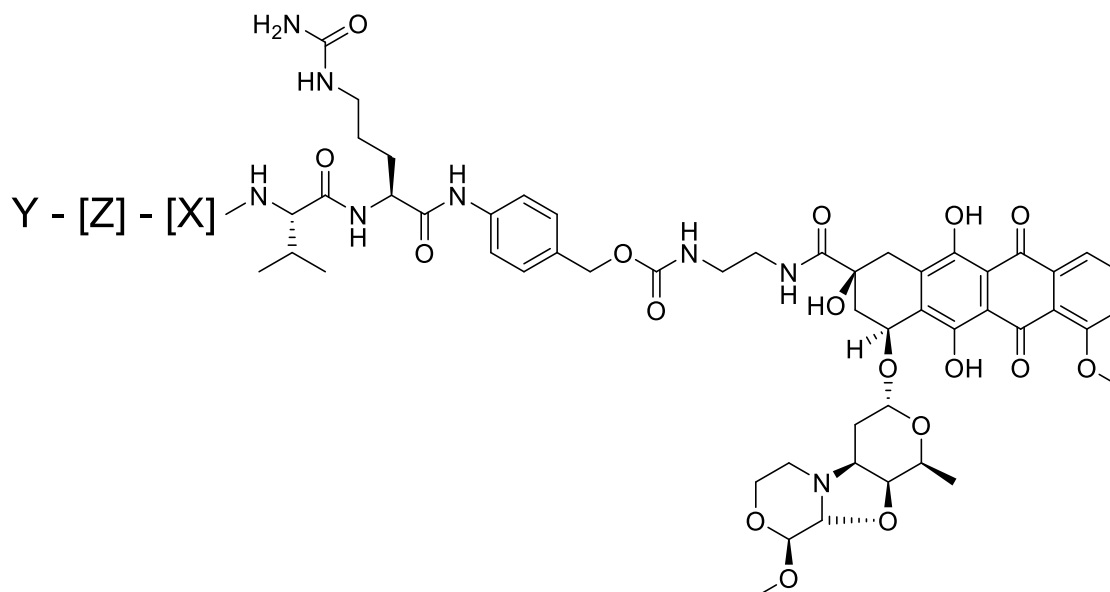
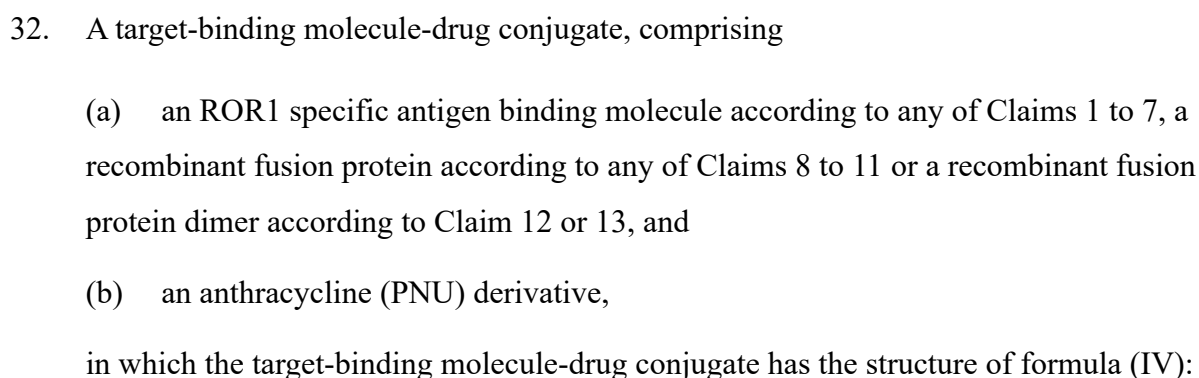
in which [X] is an optional spacer selected from the group comprising substituted or unsubstituted alkyl groups, substituted or unsubstituted heteroalkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heteroaryl groups, one or more heteroatoms, polyethylene glycol or a 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 ROR1 specific antigen binding molecule according to any of Claims 1 to 7, a recombinant fusion protein according to any of Claims 8 to 11 or a recombinant fusion protein dimer according to any of Claims 12 or 13, optionally in which:

- (a) the target-binding molecule-drug conjugate of formula (III) comprises [L1], [L2] or [L1] and [L2], further optionally in which [L2] is p-aminobenzyloxycarbonyl (PAB) or alanine; or
- (b) the target-binding molecule-drug conjugate has a structure selected from:





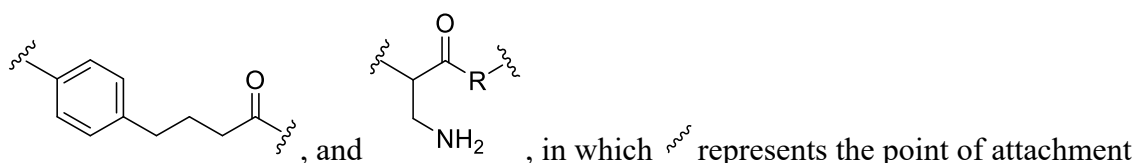
in which [X] is an optional spacer selected from the group comprising substituted or unsubstituted alkyl groups, substituted or unsubstituted heteroalkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heteroaryl groups, one or more heteroatoms, polyethylene glycol or a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

[Z] is a linker derived from a reactive group used to conjugate the anthracycline (PNU) derivative and the target-binding molecule; and

Y comprises an ROR1 specific antigen binding molecule according to any of Claims 1 to 7, a recombinant fusion protein according to any of Claims 8 to 11 or a recombinant fusion protein dimer according to Claim 12 or 13, optionally in which [Z] is selected from the group consisting of a disulphide bond, an amide bond, an oxime bond, a hydrazone bond, a thioether bond, a 1, 2, 3 triazole and polyGly.

33. A target-binding molecule-drug conjugate according to Claim 31 or 32, in which:

- (a) [X] is selected from the group comprising polyethylene glycol,



to the rest of the molecule and in which [R] 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; and/or

- (b) in which [X] is polyethylene glycol.

34. A target-binding molecule-drug conjugate according to Claim 31, 32 or 33, in which the target-binding molecule is a protein and the anthracycline (PNU) derivative is conjugated to a thiol-containing amino acid residue in the amino acid sequence of the protein, and/or in which the PNU derivative is conjugated via a thiol moiety incorporated by chemical modification at the N-terminus or C-terminus of the amino acid sequence of the protein, and/or in which Y comprises an ROR1 specific antigen binding molecule according to any of Claims 1 to 7 conjugated to the PNU derivative via a human immunoglobulin Fc region or fragment thereof.

35. A specific antigen binding molecule according to Claim 30, in which:

- (a) the specific antigen binding molecule comprises SEQ ID NO: 178 and/or SEQ ID NO: 179;

- (b) X or Y are individually either absent or selected from the group comprising 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;
- (c) the immunoglobulin Fc region is an Fc heavy chain engineered to comprise one or more cysteine residues suitable for bioconjugation;
- (d) X or Y are individually either absent or a fragment of an immunoglobulin Fc region engineered to dimerize with a second fragment of an immunoglobulin Fc region, optionally in which the method is selected from the group consisting of knobs-into-holes (Y-T), knobs-into-holes (CW-CSAV), CH3 charge pairing, Fab-arm exchange, SEED technology, BEATtechnology, HA-TF, ZW1 approach, Biclonic approach, EW-RVT and Triomab;
- (e) X or Y are individually either absent or a fragment of the immunoglobulin Fc region that comprises one or more amino acid substitution suitable for heterodimerization with a second fragment of an immunoglobulin Fc region comprising one or more corresponding amino acid mutation, optionally in which the one or more amino acid substitution is selected from the group consisting of T366Y, Y407T, S354C, T366W, Y349C, T366S, L368A and Y407V.