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

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

CDR1 is DTSYGLYS (SEQ ID NO: 1)

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

HV2 is TTDWERMSIG (SEQ ID NO: 6)

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

HV4 is NKGAK (SEQ ID NO: 11)

FW3b is a framework region of from 17 to 24 amino acids

CDR3 is REARHPWLRQWY (SEQ ID NO: 17)

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

or a sequence with at least 70% sequence identity thereto, in which the ROR1-specific antigen binding molecule

(i) does not bind to receptor tyrosine kinase-like orphan receptor 2 (ROR2),

(ii) binds to both human ROR1 and murine ROR1 (mROR1),

(iii) binds to deglycosylated ROR1, and

(iv) does not bind to a linear peptide sequence selected from:

YMESLHMQGEIENQI (SEQ ID NO: 34)

CQPWNSQYPHTHTFTALRFP (SEQ ID NO: 35)

RSTIYGSRLRIRNLDTTDTGYFQ (SEQ ID NO: 36)

QCVATNGKEVVSSTGVLFVKFGPPPTASPGYSDEYE (SEQ ID NO: 37).

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

FW1 is TRVDQTPRTATKETGESLTINCVLT (SEQ ID NO: 22), FW2 is TSWFRKNPG (SEQ ID NO: 25), FW3a is GRYVESV (SEQ ID NO: 27), FW3b is SFSLRIKDLTVADSATYYCKA (SEQ ID NO: 29) and FW4 is DGAGTVLTVN (SEQ ID NO: 32), or a sequence with a sequence identity of at least 70%.

3. An ROR1-specific antigen binding molecule according to Claim 1 or 2, in which the ROR1-specific antigen binding molecule comprises the amino acid sequence TRVDQTPRTATKETGESLTINCVLTDTSYGLYSTSWFRKNPGTTDWERMSIGGRYVES VNKGAKSFSLRIKDLTVADSATYYCKAREARHPWLRQWYDGAGTVLTVN (SEQ ID NO: 43); or a sequence with a sequence identity of at least 70%.

4. An ROR1-specific antigen binding molecule according to Claim 1, 2 or 3, in which the ROR1-specific antigen binding molecule is humanized, or in which the ROR1-specific antigen binding molecule is de-immunized.

5. 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.

6. An ROR1-specific antigen binding molecule according to any preceding claim, in which the specific antigen binding molecule selectively interacts with ROR1 protein with an affinity constant of 0.01 to 50 nM, preferably 0.1 to 30 nM, even more preferably 0.1 to 10 nM.

7. An ROR1-specific antigen binding molecule according to any preceding claim, in which the specific antigen binding molecule is capable of

(i) mediating killing of ROR1-expressing tumour cells,

(ii) inhibiting cancer cell proliferation, or

(iii) being endocytosed upon binding to ROR1.

8. A recombinant fusion protein comprising a specific antigen binding molecule according to any preceding claim.

9. A recombinant fusion protein according to Claim 8, in which the specific antigen binding molecule is fused to one or more biologically active proteins, optionally in which

(i) the specific antigen binding molecule is fused to one or more biologically active proteins via one or more linker domains, and/or

(ii) at least one biologically active protein is an immunoglobin, an immunoglobulin Fc region, an immunoglobin Fab region, a single chain Fv (scFv), a diabody, a triabody, a tetrabody, a bispecific t-cell engager (BiTE), an intein, a VNAR domain, a single domain antibody (sdAb), a VH domain, or a scaffold protein.

10. A ROR1-specific chimeric antigen receptor (CAR), comprising at least one ROR1-specific antigen binding molecule as defined in any of Claims 1 to 4, fused or conjugated to at least one transmembrane region and at least one intracellular domain.

11. A cell comprising a chimeric antigen receptor according to Claim 10, which 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 or chimeric antigen receptor according to any of Claims 1 to 10, a vector comprising the nucleic acid sequence and optionally further comprising one or more regulatory sequences, or a host cell comprising the vector.

13. 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 12 under conditions such that the host cell produces the binding molecule, optionally further comprising isolating the binding molecule.

14. A pharmaceutical composition comprising a specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor according to any of Claims 1 to 10.

15. A specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor according to any of Claims 1 to 10, for use in therapy.

16. A specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor according to any of Claims 1 to 10, for use in the treatment of cancer, optionally in which the cancer is a ROR1-positive cancer type, or 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, stomach cancer or liver cancer.

17. 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 or a recombinant fusion protein according to Claim 8 or 9 to the sample and detecting the binding of the molecule to the target analyte.

18. A method of imaging a site of disease in a subject, comprising administration of a detectably labelled specific antigen binding molecule according to any of Claims 1 to 7 or a detectably labelled recombinant fusion protein according to Claim 8 or 9 to a subject.

19. A method of diagnosis of a disease or medical condition in a subject comprising administration of a detectably labelled specific antigen binding molecule according to any of Claims 1 to 7 or a recombinant fusion protein according to Claim 8 or 9 to the subject and detecting the molecule.

20. 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 a ROR1-specific antigen binding molecule as defined in any of Claims 1 to 7, a recombinant fusion protein as defined in Claim 8 or 9, a CAR as defined in Claim 10, or a nucleic acid as defined in Claim 12, each being optionally derivatized, in which presence of antigen in the sample suggests that the subject suffers from cancer, optionally in which

(i) the antigen comprises ROR1 protein, more preferably an extracellular domain thereof,

(ii) 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,

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

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

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

X-FW1-CDR1-FW2-HV2-FW3a-HV4-FW3b-CDR3-FW4-Y (II)

in which

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

CDR1 is DTSYGLYS (SEQ ID NO: 1)

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

HV2 is TTDWERMSIG (SEQ ID NO: 6)

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

HV4 is NKGAK (SEQ ID NO: 11)

FW3b is a framework region of from 17 to 24 amino acids

CDR3 is REARHPWLRQWY (SEQ ID NO: 17)

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

X and Y are optional amino acid sequences

in which the specific antigen binding molecule is conjugated to a second moiety, or a sequence with at least 70% sequence identity thereto, in which

(i) the ROR1-specific antigen binding molecule does not bind to receptor tyrosine kinase-like orphan receptor 2 (ROR2),

(ii) the ROR1-specific antigen binding molecule binds to both human ROR1 and murine ROR1 (mROR1),

(iii) the ROR1-specific antigen binding molecule binds to deglycosylated ROR1, and

(iv) the ROR1-specific antigen binding molecule does not bind to a linear peptide sequence selected from:

YMESLHMQGEIENQI (SEQ ID NO: 34)

CQPWNSQYPHTHTFTALRFP (SEQ ID NO: 35)

RSTIYGSRLRIRNLDTTDTGYFQ (SEQ ID NO: 36)

QCVATNGKEVVSSTGVLFVKFGPPPTASPGYSDEYE (SEQ ID NO: 37).

22. A specific antigen binding molecule according to Claim 21, in which X or Y are individually either absent or selected from the group comprising an immunoglobulin, an immunoglobulin Fc region, an immunoglobulin Fab region, a single chain Fv (scFv), a diabody, a triabody, a tetrabody, a bispecific t-cell engager (BiTE), an intein, a VNAR domain, a single domain antibody (sdAb), a VH domain, or a scaffold protein.

23. A specific antigen binding molecule according to Claim 21 or 22, in which

(i) the conjugation is via a cysteine residue in the amino acid sequence of the specific antigen binding molecule, or the conjugation is via a thiol, aminoxy or hydrazinyl moiety incorporated at the N-terminus or C-terminus of the amino acid sequence of the specific antigen binding molecule, and/or

(ii) the second moiety is selected from the group comprising an immunoglobulin, an immunoglobulin Fc region, an immunoglobulin Fab region, a single chain Fv (scFv), a diabody, a triabody, a tetrabody, a bispecific t-cell engager (BiTE), an intein, a VNAR domain, a single domain antibody (sdAb), a VH domain, a scaffold protein, detectable label, dye, toxin, drug, pro-drug, radionuclide, biologically active molecule, or at least one toxin selected from the group comprising:

- maytansinoids,
- auristatins,
- anthracyclins, preferably PNU-derived anthracyclins
- 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

24. A specific antigen binding molecule according to Claim 21, 22 or 23, in which:

(i) FW1 is TRVDQTPRTATKETGESLTINCVLT (SEQ ID NO: 22), FW2 is TSWFRKNPG (SEQ ID NO: 25), FW3a is GRYVESV (SEQ ID NO: 27), FW3b is SFSLRIKDLTVADSATYYCKA (SEQ ID NO: 29), and FW4 is DGAGTVLTVN (SEQ ID NO: 32), or a sequence with a sequence identity of at least 70%, or

(ii) the ROR1-specific antigen binding molecule comprises the amino acid sequence TRVDQTPRTATKETGESLTINCVLTDTSYGLYSTSWFRKNPGTTDWERMSIGGR YVESVNKGAKSFSLRIKDLTVADSATYYCKAREARHPWLRQWYDGAGTVLTV N (SEQ ID NO: 43); or a sequence with a sequence identity of at least 70%.

25. A specific antigen binding molecule according to any of Claims 21 to 24, in which the ROR1-specific antigen binding molecule is humanized, or the ROR1-specific antigen binding molecule is de-immunized.