

WHAT IS CLAIMED IS:

1. An isolated polypeptide that specifically binds to Ror2 protein, said polypeptide comprising a heavy chain variable region including three complementarity determining regions, said regions having H1, H2, and H3 sequences, wherein:

- (a) the H1 sequence is GYTX₁TEX₂X₃X₄H (SEQ ID NO:1) or GYSITTGX₂₉YWN (SEQ ID NO:4);
- (b) the H2 sequence is X₅X₆X₇X₈NNGGTGYNQKFKG (SEQ ID NO:2) or YITYDGSX₃₀NYNPSLKN (SEQ ID NO:5); and
- (c) the H3 sequence is X₉X₁₀X₁₁SX₁₂YX₁₃YX₁₄X₁₅SYFX₁₆X₁₇X₁₈ (SEQ ID NO:3) or CSX₃₁X₃₂X₃₃X₃₄VX₃₅X₃₆X₃₇LDX₃₈ (SEQ ID NO:6);

wherein

- X₁ is F or E,
- X₂ is Y or D,
- X₃ is T or C,
- X₄ is M or D or E or Y,
- X₅ is G or S,
- X₆ is I or E,
- X₇ is N or C or L or V,
- X₈ is T or D or E,
- X₉ is A or M or T,
- X₁₀ is R or H,
- X₁₁ is G or E,
- X₁₂ is L or F,
- X₁₃ is S or G,
- X₁₄ is G or D,
- X₁₅ is N or E,
- X₁₆ is D or L,
- X₁₇ is Y or C or T,
- X₁₈ is W or L,
- X₂₉ is Y or E or R or T,
- X₃₀ is K or N,
- X₃₁ is R or G or H or W or Y,
- X₃₂ is F or C or N or Q,
- X₃₃ is E or S,

X₃₄ is G or E or F or H or M or Q or S,

X₃₅ is W or A or I or P or Q or T or V,

X₃₆ is Y or G or N or Q,

X₃₇ is G or S or T, and

X₃₈ is Y or I.

2. The polypeptide of claim 1, wherein the heavy chain variable region has an amino acid sequence selected from sequences of SEQ ID NOS: 18-26.

3. The polypeptide of any one of claims 1-2 in combination with an isolated light chain variable region including three complementarity determining regions L1, L2, and L3 sequences, wherein:

(a) the L1 sequence is SATSSX₁₉X₂₀X₂₁MX₂₂ (SEQ ID NO:7) or

RASESVDRYGNSX₃₉IH (SEQ ID NO:10);

(b) L2 sequence is X₂₃TSNLAS (SEQ ID NO:8) or X₄₀TYX₄₁LES (SEQ ID NO:11);

and

(c) L3 sequence is QX₂₄X₂₅SX₂₆YPFX₂₇X₂₈ (SEQ ID NO:9) or

QQX₄₂NX₄₃DPX₄₄TX₄₅ (SEQ ID NO:12);

wherein

X₁₉ is V or E,

X₂₀ is S or D,

X₂₁ is Y or C or D,

X₂₂ is H or G or L,

X₂₃ is G or C or H or P,

X₂₄ is Q or E,

X₂₅ is R or H,

X₂₆ is S or D or G or I or Q or V,

X₂₇ is T or D,

X₂₈ is F or D or E,

X₃₉ is F or S or T,

X₄₀ is R or C or D or E or W,

X₄₁ is N or D,

X₄₂ is T or I or P,

X₄₃ is E or V,

X₄₄ is W or T, and

X₄₅ is F or T.

4. The polypeptide of claim 3, wherein the light chain variable region has an amino acid sequence selected from SEQ ID NOS: 13-17 and 27.

5. The polypeptide of any one of claims 1-4, wherein the X₂₉ is Y.

6. The polypeptide of any one of claims 1-4, wherein the X₂₉ is E.

7. An isolated polypeptide that specifically binds to Ror2 protein, said polypeptide comprising an light chain variable region including three complementarity determining regions having L1, L2, and L3 sequences, wherein:

(a) the L1 sequence is SATSSX₁₉X₂₀X₂₁MX₂₂ (SEQ ID NO:7) or

RASESVDRYGNSX₃₉IH (SEQ ID NO:10);

(b) the L2 sequence is X₂₃TSNLAS (SEQ ID NO:8) or X₄₀TYX₄₁LES (SEQ ID NO:11); and

(c) the L3 sequence is QX₂₄X₂₅SX₂₆YPFX₂₇X₂₈ (SEQ ID NO:9) or

QQX₄₂NX₄₃DPX₄₄TX₄₅ (SEQ ID NO:12);

wherein

X₁₉ is V or E,

X₂₀ is S or D,

X₂₁ is Y or C or D,

X₂₂ is H or G or L,

X₂₃ is G or C or H or P,

X₂₄ is Q or E,

X₂₅ is R or H,

X₂₆ is S or D or G or I or Q or V,

X₂₇ is T or D,

X₂₈ is F or D or E,

X₃₉ is F or S or T,

X₄₀ is R or C or D or E or W,

X₄₁ is N or D,

X₄₂ is T or I or P,

X₄₃ is E or V,
X₄₄ is W or T, and
X₄₅ is F or T.

8. The polypeptide of claim 7, wherein the light chain variable region is encoded by a DNA sequence selected from SEQ ID NOS: 13-17 and 27.
9. The polypeptide of claim 7, wherein the light chain variable region including three complementarity determining regions L1, L2, and L3 having sequences of SEQ ID NOS: 10-12 respectively.
10. An anti-Ror2 antibody or antibody fragment comprising the isolated heavy chain variable region polypeptide of claim 1.
11. The antibody or antibody fragment of claim 10, further comprising an isolated light chain variable region comprising three complementarity determining regions L1, L2, and L3 sequences, wherein:
- (a) the L1 sequence is SATSSX₁₉X₂₀X₂₁MX₂₂ (SEQ ID NO:7) or RASESVDRYGNSX₃₉IH (SEQ ID NO:10);
 - (b) the L2 sequence is X₂₃TSNLAS (SEQ ID NO:8) or X₄₀TYX₄₁LES (SEQ ID NO:11); and
 - (c) the L3 sequence is QX₂₄X₂₅SX₂₆YPFX₂₇X₂₈ (SEQ ID NO:9) or QQX₄₂NX₄₃DPX₄₄TX₄₅ (SEQ ID NO:12);
- wherein
- X₁₉ is V or E,
X₂₀ is S or D,
X₂₁ is Y or C or D,
X₂₂ is H or G or L,
X₂₃ is G or C or H or P,
X₂₄ is Q or E,
X₂₅ is R or H,
X₂₆ is S or D or G or I or Q or V,
X₂₇ is T or D,
X₂₈ is F or D or E,

X₃₉ is F or S or T,
X₄₀ is R or C or D or E or W,
X₄₁ is N or D,
X₄₂ is T or I or P,
X₄₃ is E or V,
X₄₄ is W or T, and
X₄₅ is F or T.

12. The antibody or antibody fragment of any one of claims 10-11, wherein the antibody or antibody fragment has a higher binding affinity to Ror2 protein at a value of a condition in a tumor microenvironment in comparison with a different value of the same condition that occurs in a non-tumor microenvironment.
13. The antibody or antibody fragment of claim 12, wherein the condition is pH.
14. The antibody or antibody fragment of claim 13, wherein the pH in the tumor microenvironment is in a range of from 5.8 to 6.8 and the pH in the non-tumor microenvironment is in a range of 7.0 to 7.6.
15. The antibody or antibody fragment of any one of claims 10-14, wherein the antibody or antibody fragment has a ratio of binding affinity to the Ror2 protein at a value of a condition in a tumor microenvironment to a binding affinity to the Ror2 protein at a different value of the same condition in a non-tumor microenvironment of at least about 1.5:1, at least about 2:1, at least about 3:1, at least about 4:1, at least about 5:1, at least about 6:1, at least about 7:1, at least about 8:1, at least about 9:1, at least about 10:1, at least about 20:1, at least about 30:1, at least about 50:1, at least about 70:1, or at least about 100:1.
16. The antibody or antibody fragment of any of one of claims 10-15, wherein the antibody or antibody fragment is a chimeric antibody, a multispecific antibody, or a humanized antibody.
17. An immunoconjugate comprising the antibody or antibody fragment of any one of claims 10-16.

18. The immunoconjugate of claim 17, wherein the immunoconjugate comprises at least one agent selected from a chemotherapeutic agent, a radioactive atom, a cytostatic agent and a cytotoxic agent.
19. The immunoconjugate of claim 18, comprising at least two said agents.
20. The immunoconjugate of any one of claims 18-19, wherein the antibody or antibody fragment and the at least one agent are covalently bonded to a linker molecule.
21. The immunoconjugate of any one of claims 18-20, wherein the at least one agent is selected from maytansinoids, auristatins, dolastatins, calicheamicin, pyrrolobenzodiazepines, and anthracyclines.
22. A pharmaceutical composition comprising:
the polypeptide of any one of claims 1-9, the antibody or antibody fragment of any one of claims 10-16, or the immunoconjugate of any one of claims 14-18; and
a pharmaceutically acceptable carrier.
23. The pharmaceutical composition of claim 22, further comprising a tonicity agent.
24. A method of treating cancer comprising a step of administering the pharmaceutical composition of any one of claims 22-23 to a patient with cancer.
25. A kit for diagnosis or treatment, said kit comprising the polypeptide of any one of claims 1-9, the antibody or antibody fragment of any one of claims 10-16, or the immunoconjugate of any one of claims 17-21, or the pharmaceutical composition of any one of claims 22-23 and instructions for using the antibody or antibody fragment, the immunoconjugate and/or the pharmaceutical composition for diagnosis or treatment.