

WHAT IS CLAIMED IS:

1. An isolated polypeptide that specifically binds to Axl 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 $X_1GX_2X_3MX_4$ (SEQ ID NO: 1);
- (b) the H2 sequence is $LIKX_5SNGGTGX_6YNQKFKG$ (SEQ ID NO: 2); and
- (c) the H3 sequence is $GX_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}DYX_{15}X_{16}$ (SEQ ID NO: 3),

wherein

- X_1 is T or A or W,
- X_2 is H or A,
- X_3 is T or I,
- X_4 is N or I,
- X_5 is P or N,
- X_6 is S or I or T,
- X_7 is H or D or E or P or R or W,
- X_8 is Y or N,
- X_9 is E or A or D or F or G or H or I or L or M or N or R or V or Y,
- X_{10} is S or D or M or N or Q,
- X_{11} is Y or C or E or P,
- X_{12} is F or E or N or S or T or V,
- X_{13} is A or D or G or L or Y,
- X_{14} is M or E or F,
- X_{15} is W or A or D or H or L or N or P or R or T, and
- X_{16} is G or H.

2. The polypeptide of claim 1, wherein the heavy chain variable region is encoded by a DNA sequence selected from sequences of SEQ ID NOS: 11-13.

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 $KASQDX_{17}X_{18}SX_{19}VX_{20}$ (SEQ ID NO: 4);
- (b) the L2 sequence is $X_{21}X_{22}X_{23}TRX_{24}T$ (SEQ ID NO: 5); and

(c) the L3 sequence is QEX₂₅X₂₆SX₂₇X₂₈X₂₉X₃₀ (SEQ ID NO: 6),

wherein

X₁₇ is V or D or G or N or W,

X₁₈ is S or V,

X₁₉ is A or L or M,

X₂₀ is A or D or N or Q,

X₂₁ is W or F,

X₂₂ is A or I or N or P or Q,

X₂₃ is S or D,

X₂₄ is H or D,

X₂₅ is H or C or F or I or L or Q or S or T or V or Y,

X₂₆ is F or C or D or E or G or N or S,

X₂₇ is T or C or P,

X₂₈ is P or A or C or D or E or H or K or S or T or V or W,

X₂₉ is L or G or R, and

X₃₀ is T or I or R.

4. The polypeptide of claim 3, wherein the light chain variable region is encoded by a DNA sequence selected from SEQ ID NOS: 7-10.

5. An isolated polypeptide that specifically binds to Axl 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 KASQDX₁₇X₁₈SX₁₉VX₂₀ (SEQ ID NO: 4);

(b) the L2 sequence is X₂₁X₂₂X₂₃TRX₂₄T (SEQ ID NO: 5); and

(c) the L3 sequence is QEX₂₅X₂₆SX₂₇X₂₈X₂₉X₃₀ (SEQ ID NO: 6),

wherein

X₁₇ is V or D or G or N or W,

X₁₈ is S or V,

X₁₉ is A or L or M,

X₂₀ is A or D or N or Q,

X₂₁ is W or F,

X₂₂ is A or I or N or P or Q,

X₂₃ is S or D,

X₂₄ is H or D,

X₂₅ is H or C or F or I or L or Q or S or T or V or Y,

X₂₆ is F or C or D or E or G or N or S,

X₂₇ is T or C or P,

X₂₈ is P or A or C or D or E or H or K or S or T or V or W,

X₂₉ is L or G or R, and

X₃₀ is T or I or R.

6. The polypeptide of claim 5, wherein the light chain variable region is encoded by a DNA sequence selected from SEQ ID NOS: 7-10.

7. An anti-Axl antibody or antibody fragment comprising the isolated heavy chain variable region polypeptide of claim 1.

8. The antibody or antibody fragment of claim 7, further comprising an isolated light chain variable region comprising three complementarity determining regions L1, L2, and L3 sequences, wherein:

(a) the L1 sequence is KASQDX₁₇X₁₈SX₁₉VX₂₀ (SEQ ID NO: 4);

(b) the L2 sequence is X₂₁X₂₂X₂₃TRX₂₄T (SEQ ID NO: 5); and

(c) the L3 sequence is QEX₂₅X₂₆SX₂₇X₂₈X₂₉X₃₀ (SEQ ID NO: 6),

wherein

X₁₇ is V or D or G or N or W,

X₁₈ is S or V,

X₁₉ is A or L or M,

X₂₀ is A or D or N or Q,

X₂₁ is W or F,

X₂₂ is A or I or N or P or Q,

X₂₃ is S or D,

X₂₄ is H or D,

X₂₅ is H or C or F or I or L or Q or S or T or V or Y,

X₂₆ is F or C or D or E or G or N or S,

X₂₇ is T or C or P,

X₂₈ is P or A or C or D or E or H or K or S or T or V or W,

X₂₉ is L or G or R, and

X₃₀ is T or I or R.

9. The antibody or antibody fragment of any one of claims 7-8, wherein the antibody or antibody fragment has a higher binding affinity to Axl 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.
10. The antibody or antibody fragment of claim 9, wherein the condition is pH.
11. The antibody or antibody fragment of claim 10, wherein the pH in the tumor microenvironment is in a range of from 5.8 to 7.0 and the pH in the non-tumor microenvironment is in a range of 7.0-7.6.
12. The antibody or antibody fragment of any one of claims 7-11, wherein the antibody or antibody fragment has a ratio of binding affinity to the Axl protein at a value of a condition in a tumor microenvironment and a binding affinity to the Axl 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.
13. The antibody or antibody fragment of any one of claims 7-12, wherein the antibody or antibody fragment is a chimeric antibody, a multispecific antibody, or a humanized antibody.
14. An immunoconjugate comprising the antibody or antibody fragment of any one of claims 7-13.
15. The immunoconjugate of claim 14, wherein the immunoconjugate comprises at least one agent selected from a chemotherapeutic agent, a radioactive atom, a cytostatic agent and a cytotoxic agent.
16. The immunoconjugate of claim 15, comprising at least two said agents.

17. The immunoconjugate of any one of claims 15-16, wherein the antibody or antibody fragment and the at least one agent are covalently bonded to a linker molecule.
18. The immunoconjugate of any one of claims 15-17, wherein the at least one agent is selected from maytansinoids, auristatins, dolastatins, calicheamicin, pyrrolobenzodiazepines, and anthracyclines.
19. A pharmaceutical composition comprising:
the polypeptide of any one of claims 1-6, the antibody or antibody fragment of any one of claims 7-13, or the immunoconjugate of any one of claims 14-18; and
a pharmaceutically acceptable carrier.
20. The pharmaceutical composition of claim 19, further comprising a tonicity agent.
21. A method of treating cancer comprising a step of administering the pharmaceutical composition of any one of claims 19-20 to a patient with cancer.
22. A kit for diagnosis or treatment, said kit comprising the polypeptide of any one of claims 1-6, the antibody or antibody fragment of any one of claims 7-13, or the immunoconjugate of any one of claims 14-18, or the pharmaceutical composition of any one of claims 19-20 and instructions for using the antibody or antibody fragment, the immunoconjugate and/or the pharmaceutical composition for diagnosis or treatment.