

What is claimed: Claims

1. An isolated Interleukin-38 (IL-38)-binding antibody, or antigen-binding fragment thereof, comprising at least 3, at least 4, at least 5, at least 6, at least 7, or at least 8 optionally contiguous amino acids of at least one complementary-determining region (CDR) contained within the variable heavy chain (VH) amino acid sequences of: SEQ ID NO: 22, SEQ ID NO: 27, SEQ ID NO: 32, SEQ ID NO: 37, SEQ ID NO: 42, SEQ ID NO: 47, SEQ ID NO: 52, SEQ ID NO: 2, or SEQ ID NO: 7; and/or contained within the variable light chain (VL) amino acid sequences of: SEQ ID NO: 57, SEQ ID NO: 62, SEQ ID NO: 67, SEQ ID NO: 72, SEQ ID NO: 77, SEQ ID NO: 82, SEQ ID NO: 4, or SEQ ID NO: 9.

2. The IL-38-binding antibody, or antigen-binding fragment thereof, of claim 1, comprising:

a VH CDR1, a VH CDR2 and a VH CDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:22 and a VL CDR1, VL CDR2 and a VL CDR3 of a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:57;

a VH CDR1, a VH CDR2 and a VH CDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:7 and a VL CDR1, VL CDR2 and a VL CDR3 of a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:9;

a VH CDR1, a VH CDR2 and a VH CDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:27 and a VL CDR1, VL CDR2 and a VL CDR3 of a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:57;

a VH CDR1, a VH CDR2 and a VH CDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:37 and a VL CDR1, VL CDR2 and a VL CDR3 of a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:67;

a VH CDR1, a VH CDR2 and a VH CDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:42 and a VL CDR1, VL CDR2 and a VL CDR3 of a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:72;

a VH CDR1, a VH CDR2 and a VH CDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:47 and a VL CDR1, VL CDR2 and a VL CDR3 of a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:77;

a VH CDR1, a VH CDR2 and a VH CDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:32 and a VL CDR1, VL CDR2 and a VL CDR3 of a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:62;

a VH CDR1, a VH CDR2 and a VH CDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:52 and a VL CDR1, VL CDR2 and a VL CDR3 of a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:82; or

a VH CDR1, a VH CDR2 and a VH CDR3 of a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:2 and a VL CDR1, VL CDR2 and a VL CDR3 of a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:4.

23. The isolated IL-38-binding antibody, or antigen-binding fragment thereof of claim 1 or 2, wherein the CDRs are defined by the *North* method or by the *Kabat* method.

34. An antibody, or antigen-binding fragment thereof, comprising:

at least 3, at least 4, at least 5, at least 6, at least 7, or at least 8 amino acids of:

the VH CDR1 are selected from the amino acid sequences of SEQ ID NOS: 23, 28, 33, 38, 43, 48, 53, or 15;

the VH CDR2 are selected from the amino acid sequences of SEQ ID NOS: 24, 29, 34, 39, 44, 49, 54, or 16;

the VH CDR3 are selected from the amino acid sequences of SEQ ID NOS: 25, 30, 35, 40, 45, 50, 55, or 17;

the VL CDR1 are selected from the amino acid sequences of SEQ ID NOS: 58, 63, 68, 73, 78, 83, or 18;

the VL CDR2 are selected from the amino acid sequences of SEQ ID NOS: 59, 64, 69, 74, 79, 84, or 19;
and

the VL CDR3 are selected from the amino acid sequences of SEQ ID NOS: 60, 65, 70, 75, 80, 85, or 20.

5. An antibody, or antigen-binding fragment thereof, comprising:

the VH CDR1 are selected from the amino acid sequences of SEQ ID NOS: 23, 28, 33, 38, 43, 48, 53, or 15;

the VH CDR2 are selected from the amino acid sequences of SEQ ID NOS: 24, 29, 34, 39, 44, 49, 54, or 16;

the VH CDR3 are selected from the amino acid sequences of SEQ ID NOS: 25, 30, 35, 40, 45, 50, 55, or 17;

the VL CDR1 are selected from the amino acid sequences of SEQ ID NOS: 58, 63, 68, 73, 78, 83, or 18;

the VL CDR2 are selected from the amino acid sequences of SEQ ID NOS: 59, 64, 69, 74, 79, 84, or 19;
and

the VL CDR3 are selected from the amino acid sequences of SEQ ID NOS: 60, 65, 70, 75, 80, 85, or 20.

46. The antibody, or antigen-binding fragment thereof, of claim 34 or 5, comprising at least one CDR selected from: a VH CDR1 ~~of comprising the amino acid sequence set forth in~~ SEQ ID NO: 33, a VH CDR2 of SEQ ID NO: 34, a VH CDR3 of SEQ ID NO: 35, a VL CDR1 of SEQ ID NO: 63, a VL CDR2 of SEQ ID NO: 64, and a VL CDR3 of SEQ ID NO: 65.

7. The antibody, or antigen-binding fragment thereof, of claim 4 or 5, comprising a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO:33, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO:34, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 35, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO:63, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO:64, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO:65.

58. The antibody, or antigen-binding fragment thereof, of claim 34 or 5, comprising at least one CDR selected from: a VH CDR1 ~~of comprising the amino acid sequence set forth in~~ SEQ ID NO: 38, a VH CDR2 of SEQ ID NO: 39, a VH CDR3 of SEQ ID NO: 40, a VL CDR1 of SEQ ID NO: 68, a VL CDR2 of SEQ ID NO: 69, and a VL CDR3 of SEQ ID NO: 70.

9. The antibody, or antigen-binding fragment thereof, of claim 4 or 5, comprising a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO:38, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO:39, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 40, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO:68, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO:69, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO:70.

610. ____ The antibody, or antigen-binding fragment thereof, of claim 34 or 5, comprising at least one CDR selected from: a VH CDR1 ~~of comprising the amino acid sequence set forth in~~ SEQ ID NO: 43, a VH CDR2 of SEQ ID NO: 44, a VH CDR3 of SEQ ID NO: 45, a VL CDR1 of SEQ ID NO: 73, a VL CDR2 of SEQ ID NO: 74, and a VL CDR3 of SEQ ID NO: 75.

11. The antibody, or antigen-binding fragment thereof, of claim 4 or 5, comprising a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO:43, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO:44, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 45, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO:73, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO:74, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO:75.

712. The antibody, or antigen-binding fragment thereof, of claim ~~34~~ or 5, comprising at least one CDR selected from: a VH CDR1 ~~of comprising the amino acid sequence set forth in SEQ ID NO: 48~~, a VH CDR2 of SEQ ID NO: 49, a VH CDR3 of SEQ ID NO: 50, a VL CDR1 of SEQ ID NO: 78, a VL CDR2 of SEQ ID NO: 79, and a VL CDR3 of SEQ ID NO: 80.

13. The antibody, or antigen-binding fragment thereof, of claim 4 or 5, comprising a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO:48, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO:49, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 50, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO:78, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO:79, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO:80.

814. The antibody, or antigen-binding fragment thereof, of claim ~~34~~ or 5, comprising at least one CDR selected from: a VH CDR1 ~~of comprising the amino acid sequence set forth in SEQ ID NO: 53~~, a VH CDR2 of SEQ ID NO: 54, a VH CDR3 of SEQ ID NO: 55, a VL CDR1 of SEQ ID NO: 83, a VL CDR2 of SEQ ID NO: 84, and a VL CDR3 of SEQ ID NO: 85.

15. The antibody, or antigen-binding fragment thereof, of claim 4 or 5, comprising a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO:53, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO:54, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 55, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO:83, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO:84, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO:85.

916. The antibody, or antigen-binding fragment thereof, of claim ~~34~~ or 5, comprising at least one CDR selected from: a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 15, a

VH CDR2 of SEQ ID NO: 16, a VH CDR3 of SEQ ID NO: 17, a VL CDR1 of SEQ ID NO: 18, a VL CDR2 of SEQ ID NO: 19, and a VL CDR3 of SEQ ID NO: 20.

17. The antibody, or antigen-binding fragment thereof, of claim 4 or 5, comprising a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO:15, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO:16, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 17, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO:18, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO:19, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO:20.

~~10~~18. The IL-38-binding antibody, or antigen-binding fragment of any one of claims 1-~~9~~17, wherein the IL-38 is a component of a multi-protein complex.

~~11~~19. The IL-38-binding antibody, or antigen-binding fragment of any one of claims 1-~~10~~18, wherein the antibody, or antigen-binding fragment partially or fully blocks, inhibits, or neutralizes a biological activity of IL-38.

~~12~~20. The IL-38-binding antibody or antigen-binding fragment of any one of claims 1-~~11~~19, wherein the antibody binds to IL-38 ~~is~~ present in a body fluid.

~~13~~21. The IL-38-binding antibody or antigen-binding fragment of claim ~~12~~20, wherein the body fluid is blood or a blood derivative.

~~14~~22. The IL-38-binding antibody or antigen-binding fragment of claim ~~13~~21, wherein the blood derivative is plasma or serum.

~~15~~23. The IL-38-binding antibody or antigen-binding fragment of any one of claims 1-~~14~~22, wherein the antibody binds to IL-38 ~~is~~ associated with an extracellular matrix ("ECM"), or ECM protein.

~~16~~24. The IL-38-binding antibody or antigen-binding fragment of claim ~~15~~23, wherein the antibody binds to IL-38 ~~is~~ present in a tumor micro-environment.

~~17~~25. The antigen-binding fragment of any one of claims 1-~~16~~24, wherein the antigen-binding fragment is an isolated variable heavy (VH) single domain monoclonal antibody.

~~1826.~~ The antigen-binding fragment of any one of claims 1-~~1625~~, wherein the antigen-binding fragment is a single chain (sc)Fv-Fc fragment.

~~1927.~~ The antigen-binding fragment of any one of claims 1-~~1626~~, wherein the isolated antigen-binding fragment comprises an Fv, scFv, Fab, F(ab')₂, or Fab' fragment, diabody, or any fragment whose half-life may have been increased.

~~2028.~~ The antibody or antigen-binding fragment of any one of ~~the~~ claims 1-~~1927~~, wherein the antibody or antigen-binding fragment comprises a CH3 scaffold, comprising at least one modification of the wild-type amino acid sequence of the CH3 domain derived from an immunoglobulin Fc region.

~~2129.~~ The antibody or antigen-binding fragment of any one of claims 1-~~2028~~, wherein the antibody or antigen-binding fragment is monoclonal.

~~2230.~~ The antibody or antigen-binding fragment of any one of claims 1-~~2129~~, wherein the antibody or antigen-binding fragment is human, humanized, or bi-specific.

31. A composition comprising the antibody or an antigen-binding fragment of any of claims 1-30 for use in therapy.

~~2332. A method of inhibiting tumor growth or metastasis in a subject, comprising administering to the subject a therapeutically effective amount of~~ Use of a composition comprising the antibody or an antigen-binding fragment of any of claims 1-~~2230~~ in the manufacture of a medicament for inhibiting tumor growth or metastasis in a subject, wherein a therapeutically effective amount of the composition is to be administered to a subject, and wherein the antibody or an antigen-binding fragment partially or fully blocks, inhibits, or neutralizes a biological activity of IL-38.

33. Use of the antibody or an antigen-binding fragment of any of claims 1-30 for the manufacture of a medicament for treating cancer in a subject.