

What is claimed:

1. Use of a composition comprising an antibody that binds to IL-38 in the manufacture of a medicament for treating cancer in an individual, wherein the antibody comprises

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:98 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:101;

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:10;

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:87 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:92;

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.

2. The use of claim 1, wherein the antibody comprises

a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO:23, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO:24, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 25, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO:58, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO:59, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO:60;

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;

a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO:88, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO:89, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 90, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO:93, VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO:94, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO:95

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;

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;

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;

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 of 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;

a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 28, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 29, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 30, a VL CDR1 of SEQ ID NO: 58, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 59, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 60; or

a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 53, a VH CDR2 of 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.

3. The use of claim 1 or 2, wherein the antibody that specifically binds to IL-38 comprises
- a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:98 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:101;
 - a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:22 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:57;
 - a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:7 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:10; or
 - a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:87 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:92.

4. The use of any one of claims 1-3, wherein the antibody that specifically binds to IL-38 comprises

a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO:23, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO:24, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 25, a VL CDR1 comprising the amino acid sequence set forth in

SEQ ID NO:58, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO:59, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO:60;

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; or

a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO:88, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO:89, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 90, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO:93, VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO:94, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO:95.

5. The use of claim 4, wherein the antibody that specifically binds to IL-38 comprises a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO:23, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO:24, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 25, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO:58, a VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO:59, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO:60.

6. The use of claim 5, wherein the antibody that specifically binds to IL-38 comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:98 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:101.

7. The use of any one of claims 1, 2, 4, or 5, wherein the CDRs are defined by the North method or the Kabat method.

8. The use of any one of claims 1-7, wherein the antibody that specifically binds to IL-38 is a humanized antibody.

9. The use of any one of claims 1-7, wherein the antibody that specifically binds to IL-38 is a human antibody.

10. The use of any one of claims 1-9, wherein the cancer expresses a high level of IL-38.
11. The use of any one of claims 1-10, wherein the antibody that specifically binds to IL-38 partially or fully blocks, inhibits, or neutralizes a biological activity of IL-38.
12. The use of any one of claims 1-11, wherein the individual is human.
13. The use of any one of claims 1-12, wherein the level of one or more proinflammatory cytokines is increased.
14. The use of any one of claims 1-13, wherein the level of one or more of IL-6, CCL4, CCL3, CXCL1, CXCL10, or GM-CSF is increased.
15. The use of any one of claims 1-14, wherein the cancer is a stage I, stage II, stage III, or stage IV cancer.
16. The use of any one of claims 1-15, wherein the antibody that specifically binds to IL-38 is to be administered at a dose of about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 10 mg/kg, about 15 mg/kg, about 25 mg/kg, 30 mg/kg, about 15 mg/kg, or about 50 mg/kg.
17. The use of any one of claims 1-16, wherein the antibody that specifically binds to IL-38 is a bispecific antibody.
18. The use of any one of claims 1-17, wherein the antibody that specifically binds to IL-38 is an isolated variable heavy (VH) single domain monoclonal antibody, a (sc)Fv-Fc, a Fv, a scFv, a Fab, a F(ab')₂, a Fab' fragment, a bispecific antibody, or a diabody.
19. The use of any one of claims 1-18, wherein the cancer is a squamous cell carcinoma or an adenocarcinoma.
20. The use of any one of claims 1-19, wherein the cancer is selected from the group consisting of gastroesophageal cancer, bladder cancer, cervical cancer, prostate cancer, breast cancer, renal

cancer, colorectal cancer, pancreatic cancer, melanoma, uterine cancer, head and neck cancer, lung cancer and skin cancer.

21. The use of any one of claims 1-20, wherein the cancer is selected from the group consisting of head and neck squamous cell carcinoma (HNSC), esophagus cancer (ESCA), squamous cell cancer of the lung (LUSC), cancer of the cervix (CESC), bladder cancer (BLCA), skin cutaneous melanoma (SKCM), prostate adenocarcinoma (PRAD), gastroesophageal carcinoma, cervical squamous cell carcinoma, cervical squamous cell carcinoma, skin squamous cell carcinoma, basal cell carcinoma, skin cutaneous melanoma, lung adenocarcinoma, endocervical adenocarcinoma, bladder urothelial carcinoma and prostate adenocarcinoma and lung adenocarcinoma (LUAD).

22. The use of claim 21, wherein the cancer is squamous cell cancer of the lung (LUSC).

23. The use of claim 21, wherein the cancer is gastroesophageal carcinoma.

24. The use of claim 21, wherein the cancer is head and neck squamous cell carcinoma.

25. An isolated antibody that specifically binds to IL-38 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:87 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:92.

26. The isolated antibody that specifically binds to IL-38 of claim 25, wherein the antibody comprises a VH CDR1 comprising the amino acid sequence set forth in SEQ ID NO:88, a VH CDR2 comprising the amino acid sequence set forth in SEQ ID NO:89, a VH CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 90, a VL CDR1 comprising the amino acid sequence set forth in SEQ ID NO:93, VL CDR2 comprising the amino acid sequence set forth in SEQ ID NO:94, and a VL CDR3 comprising the amino acid sequence set forth in SEQ ID NO:95.

27. An isolated antibody that specifically binds to IL-38 comprising a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:98 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:101; or

a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:87 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:92.

28. The antibody that specifically binds to IL-38 of claim 27 comprising
a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:98 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:101.

29. An isolated antibody that specifically binds to IL-38 comprising

- i) a comprises an amino acid sequence set forth in SEQ ID NO: 96, and a VL comprises an amino acid sequence set forth in SEQ ID NO: 101;
- ii) a comprises an amino acid sequence set forth in SEQ ID NO: 96, and a VL comprises an amino acid sequence set forth in SEQ ID NO: 102;
- iii) a comprises an amino acid sequence set forth in SEQ ID NO: 96, and a VL comprises an amino acid sequence set forth in SEQ ID NO: 103;
- iv) a VH comprises an amino acid sequence set forth in SEQ ID NO: 96, and a VL comprises an amino acid sequence set forth in SEQ ID NO: 104;
- v) a VH comprises an amino acid sequence set forth in SEQ ID NO: 96, and a VL comprises an amino acid sequence set forth in SEQ ID NO: 105;
- vi) a VH comprises an amino acid sequence set forth in SEQ ID NO: 96, and a VL comprises an amino acid sequence set forth in SEQ ID NO: 106;
- vii) a VH comprises an amino acid sequence set forth in SEQ ID NO: 97, and a VL comprises an amino acid sequence set forth in SEQ ID NO: 101;
- viii) a VH comprises an amino acid sequence set forth in SEQ ID NO:97, and a VL comprises an amino acid sequence set forth in SEQ ID NO: 102;
- ix) a VH comprises an amino acid sequence set forth in SEQ ID NO:97, and a VL comprises an amino acid sequence set forth in SEQ ID NO: 103;
- x) a VH comprises an amino acid sequence set forth in SEQ ID NO:97, and a VL comprises an amino acid sequence set forth in SEQ ID NO: 104;
- xi) a VH comprises an amino acid sequence set forth in SEQ ID NO:97, and a VL comprises an amino acid sequence set forth in SEQ ID NO:105;
- xii) a VH comprises an amino acid sequence set forth in SEQ ID NO:97, and a VL comprises an amino acid sequence set forth in SEQ ID NO: 106;

xiii) a VH comprises an amino acid sequence set forth in SEQ ID NO:98, and a VL comprises an amino acid sequence set forth in SEQ ID NO: 101;

xiv) a VH comprises an amino acid sequence set forth in SEQ ID NO:98, and a VL comprises an amino acid sequence set forth in SEQ ID NO:102;

xv) a VH comprises an amino acid sequence set forth in SEQ ID NO:98, and a VL comprises an amino acid sequence set forth in SEQ ID NO:103;

xvi) a VH comprises an amino acid sequence set forth in SEQ ID NO:98, and a VL comprises an amino acid sequence set forth in SEQ ID NO:104;

xvii) a VH comprises an amino acid sequence set forth in SEQ ID NO:98, and a VL comprises an amino acid sequence set forth in SEQ ID NO:105;

xviii) a VH comprises an amino acid sequence set forth in SEQ ID NO:98, and a VL comprises an amino acid sequence set forth in SEQ ID NO:106;

xix) a VH comprises an amino acid sequence set forth in SEQ ID NO:99, and a VL comprises an amino acid sequence set forth in SEQ ID NO:101;

xx) a VH comprises an amino acid sequence set forth in SEQ ID NO:99, and a VL comprises an amino acid sequence set forth in SEQ ID NO:102;

xxi) a VH comprises an amino acid sequence set forth in SEQ ID NO:99, and a VL comprises an amino acid sequence set forth in SEQ ID NO:103;

xxii) a VH comprises an amino acid sequence set forth in SEQ ID NO:99, and a VL comprises an amino acid sequence set forth in SEQ ID NO:104;

xxiii) a VH comprises an amino acid sequence set forth in SEQ ID NO:99, and a VL comprises an amino acid sequence set forth in SEQ ID NO:105;

xxiv) a VH comprises an amino acid sequence set forth in SEQ ID NO:99, and a VL comprises an amino acid sequence set forth in SEQ ID NO:106;

xxv) a VH comprises an amino acid sequence set forth in SEQ ID NO:100, and a VL comprises an amino acid sequence set forth in SEQ ID NO:101;

xxvi) a VH comprises an amino acid sequence set forth in SEQ ID NO:100, and a VL comprises an amino acid sequence set forth in SEQ ID NO:102;

xxvii) a VH comprises an amino acid sequence set forth in SEQ ID NO:100, and a VL comprises an amino acid sequence set forth in SEQ ID NO:103;

xxviii) a VH comprises an amino acid sequence set forth in SEQ ID NO:100, and a VL comprises an amino acid sequence set forth in SEQ ID NO:104;

xxix) a VH comprises an amino acid sequence set forth in SEQ ID NO:100, and a VL comprises an amino acid sequence set forth in SEQ ID NO:105; or

xxx) a VH comprises an amino acid sequence set forth in SEQ ID NO:100, and a VL comprises an amino acid sequence set forth in SEQ ID NO:106.

30. The antibody that specifically binds to IL-38 of claim 26, wherein the CDRs are defined by the North method or the Kabat method.

31. The antibody that specifically binds to IL-38 of any one of claims 25-30, wherein the antibody that specifically binds to IL-38 is a humanized antibody.

32. The antibody that specifically binds to IL-38 of any one of claims 25-31, wherein the antibody that specifically binds to IL-38 partially or fully blocks, inhibits, or neutralizes a biological activity of IL-38.

33. The antibody that specifically binds to IL-38 of any one of claims 25-32, wherein the antibody that specifically binds to IL-38 is an isolated variable heavy (VH) single domain monoclonal antibody, a (sc)Fv-Fc, a Fv, a scFv, a Fab, a F(ab')₂, a Fab' fragment, a bispecific antibody, or a diabody.

34. A composition comprising the antibody of any one of claims 25-33.

35. Nucleic acid(s) encoding the antibody of any one of claims 25-33.

36. A vector comprising the nucleic acid(s) of claim 35.

37. A host cell comprising the nucleic acid of claim 35 or the vector of claim 36.

38. The host cell of claim 37, wherein the host cell is a CHO cell.