

CLAIMS

What is claimed is:

1. An isolated antibody, or antigen-binding fragment thereof, that binds to an intracellular or transmembrane region of human CD137 ligand (CD137L), wherein the antibody or antigen-binding fragment binds to a peptide comprising the amino acid sequence of MEYASDASLDPEAPWPPAPRARACRVLP (SEQ ID NO:1) and/or binds to a peptide comprising the amino acid sequence of MEYASDASLDPEAPWPPAPRARA (SEQ ID NO:2).
2. The antibody or antigen-binding fragment of claim 1, wherein the peptide comprising the amino acid sequence of MEYASDASLDPEAPWPPAPRARACRVLP (SEQ ID NO:1) and/or the peptide comprising the amino acid sequence of MEYASDASLDPEAPWPPAPRARA (SEQ ID NO:2) is less than 50 amino acids in length.
3. The antibody or antigen-binding fragment of claim 1 or claim 2, wherein the peptide comprising the amino acid sequence of MEYASDASLDPEAPWPPAPRARACRVLP (SEQ ID NO:1) and/or the peptide comprising the amino acid sequence of MEYASDASLDPEAPWPPAPRARA (SEQ ID NO:2) does not comprise the extracellular domain of CD137L.
4. The antibody or antigen-binding fragment of any one of claims 1-3, wherein the antibody or antigen-binding fragment binds to a Chinese hamster ovary (CHO) cell that expresses human CD137L.
5. The antibody or antigen-binding fragment of any one of claims 1-4, wherein the antibody or antigen-binding fragment binds to human CD137L in a fixed human tissue sample.
6. The antibody or antigen-binding fragment of claim 5, wherein the fixed human tissue sample is a formalin-fixed paraffin-embedded (FFPE) sample.
7. The antibody or antigen-binding fragment of claim 5 or claim 6, wherein the sample is from human tonsil tissue.

8. The antibody or antigen-binding fragment of claim 5 or claim 6, wherein the sample is from human tumor tissue.

9. The antibody or antigen-binding fragment of any one of claims 1-8, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein:

(a) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO:4, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:5, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:6, and/or the light chain variable region comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO:7, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:8, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:9;

(b) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO:10, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:11, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:12, and/or the light chain variable region comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO:13, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:14, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:15;

(c) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO:16, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:17, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:18, and/or the light chain variable region comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO:19, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:20, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:21;

(d) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO:22, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:23, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:24, and/or the light chain variable region comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO:25, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:26, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:27;

(e) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO:28, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:29, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:30, and/or the light chain variable region comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO:31, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:32, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:33;

(f) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO:34, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:35, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:36, and/or the light chain variable region comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO:37, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:38, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:39;

(g) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO:40, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:41, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:42, and/or the light chain variable region comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO:43, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:44, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:45; or

(h) the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO:46, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:47, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:48, and/or the light chain variable region comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO:49, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:50, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:51.

10. The antibody or antigen-binding fragment of any one of claims 1-9, wherein:

(a) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:52, and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO:53;

(b) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:54, and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO:55;

(c) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:56, and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO:57;

(d) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:58, and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO:59;

(e) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:60, and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO:61;

(f) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:62, and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO:63;

(g) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:64, and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO:65; or

(h) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:66, and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO:67.

11. The antibody or antigen-binding fragment of any one of claims 1-10, wherein the antibody comprises a mouse IgG2a Fc region.

12. A polynucleotide encoding the antibody or antigen-binding fragment of any one of claims 1-11.

13. A vector comprising the polynucleotide of claim 12.

14. The vector of claim 13, wherein the vector is an expression vector.
15. A host cell comprising the vector of claim 13 or claim 14.
16. A method of making an antibody or antigen-binding fragment, comprising culturing the host cell of claim 15 under conditions suitable for producing the antibody or antigen-binding fragment.
17. The method of claim 16, further comprising recovering the antibody or antigen-binding fragment produced by the cell.
18. A method of detecting a level of expression of human CD137L in a sample, the method comprising:
- (a) contacting a human tissue sample with the antibody or antigen-binding fragment of any one of claims 1-11; and
 - (b) detecting binding of the antibody or antigen-binding fragment to the sample, wherein binding of the antibody or antigen-binding fragment to the sample indicates the level of expression of human CD137L in the sample.
19. The method of claim 18, wherein binding of the antibody or antigen-binding fragment to the sample is detected in ~~(be)~~ by immunohistochemistry (IHC).
20. The method of claim 18 or claim 19, ~~further comprising, prior to (a), obtaining wherein~~ a human tissue sample is to be obtained prior to (a).
21. Use of an anti-CD137 antibody in the manufacture of a medicament for~~A method of~~ treating or delaying progression of cancer in a subject in need thereof, the ~~use method~~ comprising:
- ~~(a) obtaining a sample from the individual;~~
 - ~~(ba)~~ measuring level of expression of CD137L in ~~a the~~ sample obtained from the subject using the antibody of any one of claims 1-11; and

(~~eb~~) if the level of expression of CD137L in the sample is lower than a reference level, ~~administering~~ an effective amount of ~~an anti-CD137 antibody~~ the medicament is to be administered to the ~~subject~~ individual.

22. The ~~use~~ method of claim 21, wherein the level of expression of CD137L in the sample is measured in (~~ab~~) using IHC.

23. The method of any one of claims 18-~~22~~ 20, or the use of claim 21 or claim 22, wherein the level of expression of CD137L in the sample is below the limit of detection.

24. The method of any one of claims 18-~~22~~ 20, or the use of claim 21 or claim 22, wherein the sample is a fixed sample.

25. The method or use of any one of claims 18-24, wherein the sample is a formalin-fixed paraffin-embedded (FFPE) sample.

26. The method or use of any one of claims 18-25, wherein the sample is a tumor biopsy sample.

27. The method or use of any one of claims 18-25, wherein the sample comprises one or more cancer cells.

28. The method or use of any one of claims 19-25, wherein the sample is a tumor sample from the cancer of the ~~subject~~ individual.

29. The method or use of any one of claims 18-28, wherein the level of expression of CD137L is the level of expression of CD137L by cancer cells.

30. The method or use of any one of claims 19-29, ~~further comprising administering to wherein the subject~~ a therapeutically effective amount of at least one additional therapeutic agent is to be further administered to the subject.

31. The method or use of claim 30, wherein the at least one additional therapeutic agent is selected from the group consisting of viral gene therapy, immune checkpoint inhibitor, target therapy, radiation therapy, and chemotherapy.

32. The method or use of claim 30 or claim 31, wherein the at least one additional therapeutic agent is selected from the group consisting of pomalyst, revlimid, lenalidomide, pomalidomide, thalidomide, a DNA-alkylating platinum-containing derivative, cisplatin, 5-fluorouracil, cyclophosphamide, an anti-CTLA4 antibody, an anti-PD-1 antibody, an anti-PD-L1 antibody, an anti-CD20 antibody, an anti-CD40 antibody, an anti-DR5 antibody, an anti-CD1d antibody, an anti-TIM3 antibody, an anti-SLAMF7 antibody, an anti-KIR receptor antibody, an anti-OX40 antibody, an anti-HER2 antibody, an anti-ErbB-2 antibody, an anti-EGFR antibody, cetuximab, rituximab, trastuzumab, pembrolizumab, radiotherapy, single dose radiation, fractionated radiation, focal radiation, whole organ radiation, IL-12, IFN α , GM-CSF, a chimeric antigen receptor, adoptively transferred T cells, an anti-cancer vaccine, and an oncolytic virus.