WHAT IS CLAIMED IS:

1. An antibody or antigen binding fragment thereof comprising the heavy chain variable region of any one of SEQ ID NOs: 36-40 or 73-76 and the light chain variable region of any one of SEQ ID NOs: 31-35 or 77-79.

2. The antibody or antigen binding fragment thereof of claim 1, comprising the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs: 1-3, 7-9, 13-15, 19-21, or 25-27, respectively and the LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 4-6, 10-12, 16-18, 22-24, or 28-30, respectively.

3. The antibody or antigen binding fragment thereof of claim 1 or 2, wherein the antibody is a humanized antibody.

4. The humanized antibody or antigen binding fragment thereof of claim 3, wherein the antibody is a humanized ADVH60 antibody.

5. The humanized antibody or antigen binding fragment thereof of claim 3 or 4, comprising the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs: 7-9, respectively and the LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 10-12, respectively.

6. The humanized antibody or antigen binding fragment thereof of any one of claims 3-5, wherein the humanized antibody or antigen binding fragment thereof comprises the heavy chain and the light chain of any one of:

a) SEQ ID NO: 73 and SEQ ID NO: 77, respectively;
b) SEQ ID NO: 74 and SEQ ID NO: 77, respectively;
c) SEQ ID NO: 73 and SEQ ID NO: 78, respectively;
d) SEQ ID NO: 73 and SEQ ID NO: 79, respectively;
e) SEQ ID NO: 75 and SEQ ID NO: 77, respectively;
f) SEQ ID NO: 75 and SEQ ID NO: 78, respectively;
g) SEQ ID NO: 76 and SEQ ID NO: 77, respectively; or
h) SEQ ID NO: 76 and SEQ ID NO: 78, respectively.

7. The antibody or antigen binding fragment thereof of any one of claims 1-6 for use as a medicament.

8. Use of the antibody or antigen binding fragment thereof of any one of claims 1-6 in the manufacture of a medicament for the treatment of cancer in a subject in need thereof.

9. The use of claim 8, wherein the cancer is an esophageal cancer, liver cancer, bile duct cancer, kidney cancer, thyroid cancer, bladder cancer, mesothelioma, lung cancer, melanoma, head and neck cancer, ovarian cancer, glioblastoma, malignant peripheral nerve sheath tumor, astrocytoma, pancreatic cancer, cholangiocarcinoma, stomach cancer, ALK-positive anaplastic large cell lymphoma, Ewing sarcoma, cervical cancer, or acute myeloid leukemia.

10. The use of claim 8, wherein the cancer is a squamous cancer.

11. The use of claim 10, wherein the squamous cancer is an esophageal cancer, esophageal squamous cell carcinoma, cancer of the esophagogastric junction, squamous head and neck cancer, squamous non-small cell lung cancer, or cervical cancer.

12. The use of claim 8, wherein the cancer is an esophageal cancer, lung cancer, melanoma, head and neck cancer, glioblastoma, pancreatic cancer, acute myeloid leukemia, squamous cancer, esophageal squamous cell carcinoma, squamous head and neck cancer, squamous non-small cell lung cancer, cervical cancer, or Ewing sarcoma.

13. The use of claim 9 or 12, wherein the cancer is an Ewing sarcoma.

14. The use of claim 9 or 12, wherein the cancer is an Ewing sarcoma comprising a EWSR1:FLI1 mutation.

15. The use of any one of claims 8-14, wherein the subject is a human.

16. An antibody drug conjugate comprising the formula (Ab) – [(L) – (D)m]n, or a pharmaceutically acceptable salt thereof; wherein:

(Ab) is an antibody or antigen binding fragment thereof that binds IL-1RAP, wherein the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs: 1-3, 7-9, 13-15, 19-21, or 25-27, respectively and the LCDR1, LCDR2, and LCDR3 or SEQ ID NOs: 4-6, 10-12, 16-18, 22-24, or 28-30, respectively;

(L) is a linker;

(D) is a drug moiety;

m is an integer from 1 to 8; and

n is an integer from 1 to 12,

wherein the linker (L) links (Ab) to (D).

17. The antibody drug conjugate of claim 16, wherein the antibody or antigen binding fragment thereof comprises the heavy chain variable region of any one of SEQ ID NOs: 36-40 or 73-76 and the light chain variable region of any one of SEQ ID NOs: 31-35 or 77-79.

18. The antibody drug conjugate of claims 16 or 17, wherein the antibody comprises the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs: 1-3, 7-9, 13-15, 19-21, or 25-27, respectively and the LCDR1, LCDR2, and LCDR3 or SEQ ID NOs: 4-6, 10-12, 16-18, 22-24, or 28-30, respectively.

19. The antibody drug conjugate of any one of claims 16-18, wherein the antibody is a humanized antibody.

20. The antibody drug conjugate of claim 19, comprising the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs: 7-9, respectively and the LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 10-12, respectively.

21. The antibody drug conjugate of claim 19 or 20, wherein the humanized antibody or antigen binding fragment thereof comprises the heavy chain and the light chain of any one of:

a) SEQ ID NO: 73 and SEQ ID NO: 77, respectively;

b) SEQ ID NO: 74 and SEQ ID NO: 77, respectively;

c) SEQ ID NO: 73 and SEQ ID NO: 78, respectively;

d) SEQ ID NO: 73 and SEQ ID NO: 79, respectively;

e) SEQ ID NO: 75 and SEQ ID NO: 77, respectively;

f) SEQ ID NO: 75 and SEQ ID NO: 78, respectively;

g) SEQ ID NO: 76 and SEQ ID NO: 77, respectively; or

h) SEQ ID NO: 76 and SEQ ID NO: 78, respectively.

22. The antibody drug conjugate of any one of claims 19-21, wherein the humanized antibody or antigen binding fragment thereof comprises the heavy chain and the light chain of SEQ ID NO: 75 and SEQ ID NO: 78, respectively.

23. The antibody drug conjugate of any one of claims 16-21, wherein the linker is selected from the group consisting of a cleavable linker, a non-cleavable linker, a hydrophilic linker, a procharged linker, and a dicarboxylic acid based linker.

24. The antibody drug conjugate of claim 23, wherein the linker is a cleavable linker.

25. The antibody drug conjugate of claim 24, wherein the cleavable linker is cleavable under intracellular conditions.

26. The antibody drug conjugate of claim 24 or 25, wherein the cleavable linker comprises a hydrazine group, a maleimide group, a disulfide group, a cis-aconityl group, a peptide comprising 1 to 10 amino acid residues, a para-aminobenzyl alcohol group, a photolabile group, a dimethyl group, a glucuronic acid group, or a combination thereof.

27. The antibody drug conjugate of any one of claims 24-26, wherein the cleavable linker comprises a maleimide group.

28. The antibody drug conjugate of any one of claims 25-27, wherein the cleavable linker is a peptide linker cleavable by an intracellular protease.

29. The antibody drug conjugate of any one of claims 25-28, wherein the cleavable linker is a peptide linker comprising a dipeptide, a tripeptide, a tetrapeptide, or a pentapeptide.

30. The antibody drug conjugate of claim 29, wherein the dipeptide is alanine-alanine (ala-ala), valine-alanine (val-ala), valine-glycine (val-gly), glycine-glycine (gly-gly), valine-citrulline (val-cit), alanine-phenylalanine (ala-phe), phenylalanine-lysine (phe-lys), phenylalanine-lysine (phe-lys), or N-methyl-valine-citrulline (Me-val -cit).

31. The antibody drug conjugate of claim 30, wherein the tripeptide is alanine-alanine-asparagine (ala-ala-asn), glutamic acid-valine-citrulline (glu-val-cit), glycine-valine-citrulline (glv-val-cit), or glycine-glycine-glycine (gly-gly-gly).

32. The antibody drug conjugate of claim 31, wherein the tetrapeptide is glycine-phenylalanine-leucine-glycine (gly-phe-leu-gly), glycine-glycine-phenylalanine-glycine (gly-gly-phe-gly), or alanine-leucine-alanine-leucine (ala-leu-ala-leu).

33. The antibody drug conjugate of claim 29 or 32, wherein the tetrapeptide is glycine-glycine-phenylalanine-glycine (gly-gly-phe-gly).

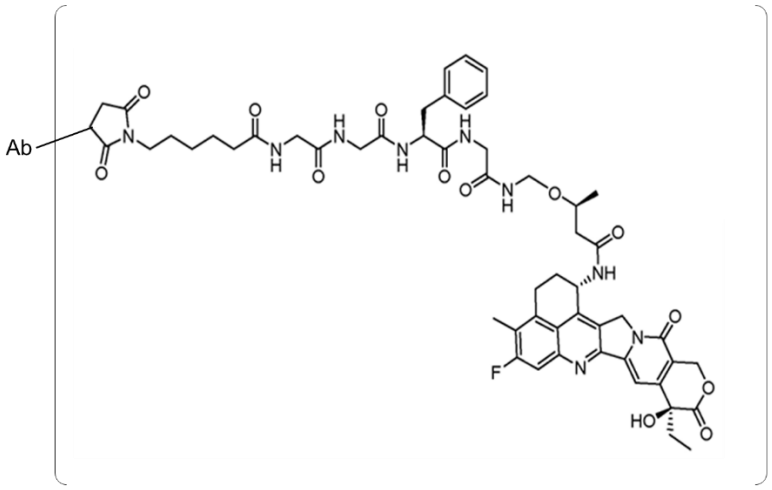
34. The antibody drug conjugate of any one of claims 16-33, wherein the drug moiety is selected from a group consisting of a V-ATPase inhibitor, a pro-apoptotic agent, a Bcl2 inhibitor, an MCL-1 inhibitor, a HSP90 inhibitor, an IAP inhibitor, an mTor inhibitor, a microtubule stabilizer, a microtubule destabilizer, a topoisomerase inhibitor, a dolastatin, a maytansinoid, a MetAP (methionine aminopeptidase), an auristatin, an amanitin, a pyrrolobenzodiazepine, an RNA polymerase inhibitor, an inhibitor of nuclear export of proteins CRM1, a DPPIV inhibitor, proteasome inhibitors, inhibitors of phosphoryl transfer reactions in mitochondria, a protein synthesis inhibitor, a kinase inhibitor, a CDK2 inhibitor, a CDK9 inhibitor, a kinesin inhibitor, an HDAC inhibitor, a DNA damaging agent, a DNA alkylating agent, a DNA intercalator, a TLR agonist, a STING agonist, a DNA minor groove binder, and a DHFR inhibitor.

35. The antibody drug conjugate of claim 34, wherein the drug moiety is a topoisomerase I inhibitor.

36. The antibody drug conjugate of claim 35, wherein the topoisomerase I inhibitor is selected from the group consisting of CHEM008, deruxtecan, camptothecins, topotecan, irinotecan, belotecan, exatecan, Exatecan mesylate, DXd, indenoisoquinolines, indotecan, indimitecan, SN-38, and lamellarin D, or their derivatives.

37. The antibody drug conjugate of claim 35 or 36, wherein the topoisomerase I inhibitor is CHEM008.

38. An antibody drug conjugate comprising the formula:



, wherein Ab comprises a humanized antibody or antigen binding fragment thereof comprising the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs: 7-9, respectively and the LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 10-12, respectively, and wherein n is an integer between 1 to 10.

39. The antibody drug conjugate of claim 38, wherein the humanized antibody or antigen binding fragment thereof comprises the heavy chain and the light chain of SEQ ID NO: 75 and SEQ ID NO: 78, respectively.

40. The antibody drug conjugate of claim 38 or 39, wherein n is 8.

41. An antibody drug conjugate comprising the formula (Ab) – [(L) – (D)m]n, or a pharmaceutically acceptable salt thereof; wherein:

(Ab) is an antibody or antigen binding fragment thereof that binds IL-1RAP, wherein the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs: 7-9, respectively and the LCDR1, LCDR2, and LCDR3 or SEQ ID NOs: 10-12, respectively;

(L) is Mc-GGFG;

(D) is CHEM008;

m is 1; and

n is 8,

wherein the linker (L) links (Ab) to (D).

42. A pharmaceutical composition comprising the antibody drug conjugate of any one of claims 16-41 and a pharmaceutically acceptable carrier.

43. A method for producing an anti-IL-1RAP antibody drug conjugate comprising: (a) chemically linking the linker as claimed in any one of claims 24-33 to the drug moiety CHEM008 to form a linker-drug; (b) conjugating the linker-drug to the antibody as claimed in any one of claims 16-22; and (c) purifying the antibody drug conjugate.

44. An antibody drug conjugate produced by the method of claim 43.

45. The antibody drug conjugate of claim 44 having a drug to antibody ratio (DAR) of about 8 as measured by UV spectrophotometry, mass spectrometry, hydrophobic interaction chromatography, reverse-phase HPLC, and/or capillary electrophoresis.

46. The antibody drug conjugate of any one of claims 16-41 or 44-45 or the pharmaceutical composition of claim 42 for use as a medicament.

47. Use of the antibody drug conjugate of any one of claims 16-41 or 44-45 or the pharmaceutical composition of claim 42 in the manufacture of a medicament for the treatment of cancer in a subject in need thereof.

48. The use of claim 47, wherein the cancer is an esophageal cancer, liver cancer, bile duct cancer, kidney cancer, thyroid cancer, bladder cancer, mesothelioma, lung cancer, melanoma, head and neck cancer, ovarian cancer, glioblastoma, malignant peripheral nerve sheath tumor, astrocytoma, pancreatic cancer, cholangiocarcinoma, stomach cancer, cervical cancer, ALK-positive anaplastic large cell lymphoma, or acute myeloid leukemia.

49. The use of claim 47, wherein the cancer is a squamous cancer.

50. The use of claim 49, wherein the squamous cancer is an esophageal cancer, esophageal squamous cell carcinoma, cancer of the esophagogastric junction, squamous head and neck cancer, squamous non-small cell lung cancer, or cervical cancer.

51. The use of claim 47, wherein the cancer is an esophageal cancer, lung cancer, melanoma, head and neck cancer, glioblastoma, pancreatic cancer, acute myeloid leukemia, squamous cancer, esophageal squamous cell carcinoma, squamous head and neck cancer, squamous non-small cell lung cancer, cervical cancer, or Ewing sarcoma.

52. The use of claim 47 or 51, wherein the cancer is an Ewing sarcoma.

53. The use of claim 47 or 51, wherein the cancer is an Ewing sarcoma comprising a EWSR1:FLI1 mutation.

54. The use of any one of claims 47-53, wherein the antibody drug conjugate induces cell death of IL-1RAP+ tumor cells and/or IL-1RAP+ tumor stromal cells.

55. The use of claim 54, wherein the antibody drug conjugate induces cell death of IL-1RAP+ tumor cells and IL-1RAP+ tumor stromal cells.

56. The use of claim 54, wherein the antibody drug conjugate induces cell death of IL-1RAP+ tumor stromal cells.

57. The use of any one of claims 54-56, wherein the IL-1RAP+ tumor stromal cells comprise tumor associated myeloid cells and/or cancer associated fibroblasts.

58. The use of any one of claims 47-57, wherein the antibody drug conjugate induces bystander killing of tumor cells which do not express IL-1RAP.

59. The use of any one claims 47-58, wherein the antibody drug conjugate or pharmaceutical composition are to be administered to the subject in combination with one or more additional therapeutic compounds.

60. The use of claim 59, wherein the subject has been pretreated with a treatment regimen comprising topoisomerase-1 and/or topisomerase 2 inhibitors.

61. The use of claim 59 or 60, wherein the subject is a topoisomerase-1 inhibitor refractory patient.

62. The use of any one of claims 59-61, wherein the one or more additional therapeutic compounds is a standard of care chemotherapeutic agent or immune checkpoint inhibitor.

63. The use of any one of claims 47-62, wherein the subject is a human.

64. The antibody drug conjugate of any one of claims 16-41 or 44-45 or the pharmaceutical composition of claim 42, wherein the drug moiety is an MCL-1 inhibitor.

65. The antibody drug conjugate or pharmaceutical composition of claim 64, wherein the MCL-1 inhibitor is selected from the group consisting of: AZD5991, S63845, AMG176, AMG397, dMCL1-2, or compound C3.

66. The antibody drug conjugate of claim 41 which is ADC019.

67. Use of the antibody drug conjugate of claim 66 in the manufacture of a medicament for the treatment of cancer in a subject in need thereof.