ANTI-DLL3 ANTIBODY AND METHOD OF MAKING AND USING THEREOF

CLAIMS

What is claimed is:

1. A Delta-Like Ligand 3 (DLL3) binding peptide having a binding specificity to human DLL3, comprising a variable heavy (VH) chain and a variable light (VL) chain,

wherein the VH chain comprises:

CDR H1 having an amino acid sequence of SEQ ID: 104, CDR H2 having an amino acid sequence of SEQ ID: 105, CDR H3 having an amino acid sequence of SEQ ID: 106,

CDR H1 having an amino acid sequence of SEQ ID: 110, CDR H2 having an amino acid sequence of SEQ ID: 111, CDR H3 having an amino acid sequence of SEQ ID: 112,

CDR H1 having an amino acid sequence of SEQ ID: 116, CDR H2 having an amino acid sequence of SEQ ID: 117, CDR H3 having an amino acid sequence of SEQ ID: 118, or

CDR H1 having an amino acid sequence of SEQ ID: 120, CDR H2 having an amino acid sequence of SEQ ID: 105, CDR H3 having an amino acid sequence of SEQ ID: 119, and

wherein the VL chain comprises:

CDR L1 having an amino acid sequence of SEQ ID: 101, CDR L2 having an amino acid sequence of SEQ ID: 102, and CDR L3 having an amino acid sequence of SEQ ID: 103,

CDR L1 having an amino acid sequence of SEQ ID: 107, CDR L2 having an amino acid sequence of SEQ ID: 108, and CDR L3 having an amino acid sequence of SEQ ID: 109,

CDR L1 having an amino acid sequence of SEQ ID: 113, CDR L2 having an amino acid sequence of SEQ ID: 114, and CDR L3 having an amino acid sequence of SEQ ID: 115, or

CDR L1 having an amino acid sequence of SEQ ID: 101, CDR L2 having an amino acid sequence of SEQ ID: 102, and CDR L3 having an amino acid sequence of SEQ ID: 121.

2. The DLL3 binding peptide of Claim 1, wherein the VH chain comprises an amino acid sequence having at least 98% sequence identify to SEQ ID NO:17, 19, 21, 23, 25, 27, 28, or 29; and wherein the VL chain comprises an amino acid sequence having at least 98% sequence identity to SEQ ID NO: 16, 18, 20, 22, 24, 26, or 30.

3. The DLL3 binding peptide of Claim 1, wherein the VH chain and the VL chain have an amino acid sequence selected from SEQ ID NOs: 17 and 16; 19 and 18; 21 and 20; 23 and 22; 25 and 24; 27 and 26; 28 and 22; 29 and 22; 29 and 30; and 28 and 30.

4. The DLL3 binding peptide of any one of Claims 1 to 3, comprising a scFv domain or Fab domain.

5. The DLL3 binding peptide of Claim 4, comprising a scFv domain, wherein the histidine residue linked to at least one end of the scFv domain; or

further comprising a Fc domain linked to the Fab domain to provide a Fab-monoFc fusion protein.

6. The DLL3 binding peptide of any one of Claims 1 to 5, comprising an amino acid sequence having at least 98% sequence identity to SEQ ID NO: 31, 32, 37, 38, 39, 40, 41, 42, 43, 44, 45, or 46.

7. An antibody having a binding specificity to human DLL3, comprising the DLL3 binding peptide of any one of claims 1 to 6.

8. The antibody of Claim 7, wherein the VH chain comprises an amino acid sequence having at least 98% sequence identify to SEQ ID NO: 17, 19, 21, 23, 25, 27, 28, or 29, and wherein the VL chain comprises an amino acid sequence having at least 98% sequence identity to SEQ ID NO: 16, 18, 20, 22, 24, 26, or 30.

9. The antibody of Claim 7 or 8, comprising a heavy chain (HC) and a light chain (LC),

wherein the HC comprises an amino acid sequence having at least 98% of sequence identity to SEQ ID NO: 37, 39, 41, 43, 45, or 31; and

wherein the LC comprises an amino acid sequence having at least 98% of sequence identity to SEQ ID NO: 32, 38, 40, 42, 44, or 46.

10. The antibody of any one of Claims 7 to 9, wherein the antibody comprises a mono-, bi- or multi-specific antibody, a purified antibody, a humanized antibody, an IgG, or a combination thereof.

11. An isolated nucleic acid sequence encoding the antibody of any one of Claims 7 to 9.

12. An expression vector or a host cell comprising the isolated nucleic acid sequences of Claim 11.

13. An immunoconjugate, comprising the antibody of any one of Claims 7 to 9 conjugated to a drug unit through a linker, wherein the linker comprises a covalent bond selected from an ester bond, an ether bond, an amine bond, an amide bond, a disulfide bond, an imide bond, a sulfone bond, a phosphate bond, a phosphorus ester bond, a peptide bond, a hydrazone bond or a combination thereof.

14. The immunoconjugate of Claim 13, wherein the drug unit comprises a unit derived from a therapeutic agent, an imaging agent, a diagnostic agent, a radioisotope, or a combination thereof.

15. The immunoconjugate of Claim 14, wherein:

(i) the therapeutic agent comprises a cytotoxic agent, a chemotherapy agent, an enzyme, an anti-estrogen agent, a receptor tyrosine kinase inhibitor, a kinase inhibitor, a cell cycle inhibitor, a DNA, RNA or protein synthesis inhibitor, a RAS inhibitor, or a combination thereof; or

(ii) the therapeutic agent comprises capecitabine, cisplatin, cyclophosphamide, methotrexate, 5-fluorouracil, Doxorubicin, cyclophosphamide, mustine, vincristine, procarbazine, prednisolone, bleomycin, vinblastine, dacarbazine, etoposide, epirubicin, pemetrexed, folinic acid, gemicitabine, oxaliplatin, irinotecan, topotecan, camptothecin, docetaxel, paclitaxel, fulvestrant, tamoxifen, letrozole, exemestane, anastrozole, aminoglutethimide, testolactone, vorozole, formestane, fadrozole, erlotinib, lafatinib, dasatinib,

gefitinib, osimertinib, vandertanib, afatinib, imatinib, pazopinib, lapatinib, sunitinib, nilotinib, sorafenib, nab-palitaxel, everolimus, temsirolimus, dabrafenib, vemurafenib, trametinib, vintafolide, apatinib, crizotinib, periforsine, olaparib, bortezomib, tofacitinib, trastuzumab, or a derivative or a combination thereof; or

(iii) the radioisotope comprises deuterium, ^{131}I, ^{32}P, ^{90}Sr, ^{90}Y, ^{89}Zr, ^{177}Lu, or a combination thereof.

16. A pharmaceutical composition, comprising the antibody of any one of Claims 7 to 9 or the immunoconjugate of any one of Claims 13 to 15 and a pharmaceutically acceptable carrier.

17. A method for producing the antibody of any one of Claims 7 to 9, comprising culturing a host cell such that the DNA sequence encoding the antibody is expressed, and purifying said antibody.

18. A method for producing the immunoconjugate of any one of Claims 13 to 15, comprising conjugating the antibody of Claim 7 with the drug unit.

19. Use of an antibody of any one of Claims 7 to 9 or the immunoconjugate of any one of Claims 13 to 15, in the manufacture of a medicament for treating or preventing a cancer, an autoimmune disease, or an infectious disease in a subject.

20. The use of Claim 19, wherein the cancer comprises lung cancer, small cell lung cancer (SCLC), large cell neuroendocrine carcinomas (LCNECs), medullary thyroid carcinomas (MTCs), cervical neuroendocrine carcinomas (CNECs), gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs), bladder cancer, bladder NENs (BMENs), prostate cancer, NE prostate cancer (NEPC), merkel cell carcinoma (MCC), breast cancer, liver cancer, hepatocellular carcinoma (HCC), glioma, pancreatic cancer, or a combination thereof.

21. The use of Claim 20, wherein the medicament is to be administered with an effective amount of a therapeutic agent, wherein the therapeutic agent comprises:

(i) an antibody, a chemotherapy agent, an enzyme, an anti-estrogen agent, a receptor tyrosine kinase inhibitor, a kinase inhibitor, a cell cycle inhibitor, a DNA, RNA or protein synthesis inhibitor, a RAS inhibitor, or a combination thereof; or

(ii) capecitabine, cisplatin, cyclophosphamide, methotrexate, 5-fluorouracil, Doxorubicin, cyclophosphamide, mustine, vincristine, procarbazine, prednisolone, bleomycin, vinblastine, dacarbazine, etoposide, epirubicin, pemetrexed, folinic acid, gemicitabine, oxaliplatin, irinotecan, topotecan, camptothecin, docetaxel, paclitaxel, fulvestrant, tamoxifen, letrozole, exemestane, anastrozole, aminoglutethimide, testolactone, vorozole, formestane, fadrozole, erlotinib, lafatinib, dasatinib, gefitinib, osimertinib, vandertanib, afatinib, imatinib, pazopinib, lapatinib, sunitinib, nilotinib, sorafenib, nab-palitaxel, everolimus, temsirolimus, Dabrafenib, vemurafenib, trametinib, vintafolide, apatinib, crizotinib, periforsine, olaparib, Bortezomib, tofacitinib, trastuzumab, or a derivative or a combination thereof.

22. The use of Claim 20 or 21, wherein the subject is a human.

23. A solution comprising an effective concentration of the antibody of any one of Claims 7 to 9 or the immunoconjugate of any one of Claims 13 to 15, wherein the solution is blood plasma obtained from a subject.