CLAIMS

What is claimed is:

1. An antibody or antigen binding fragment thereof, or a peptide having a binding specificity to human CD19, wherein the antibody or antigen binding fragment thereof, or the peptide comprises:

(a) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 1, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 13;
(b) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 3, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 15;
(c) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 5, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 17;
(d) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 7, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 19;
(e) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 9, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 21;
(f) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 11, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 23; or
(g) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 91, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 93.

2. The antibody or antigen binding fragment thereof, or a peptide of claim 1, wherein the antibody or antigen binding fragment thereof comprises a scFv or a Fab, wherein the scFv or Fab comprises:

(a) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 1, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 13;
(b) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 3, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 15;
(c) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 5, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 17;

(d) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 7, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 19;
(e) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 9, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 21;
(f) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 11, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 23; or
(g) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 91, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 93.

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

4. The antibody or antigen binding fragment thereof, or a peptide of claim 2 or 3, wherein the scFv has a binding affinity to human CD19 with a KD not greater than 10nM.

5. The antibody or antigen binding fragment thereof, or a peptide of claim 1, 2 or 4, wherein the antibody is a multi-specific antibody.

6. A multi-specific antibody-like protein comprising:

(a) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 1, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 13;
(b) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 3, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 15;
(c) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 5, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 17;
(d) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 7, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 19;
(e) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 9, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 21;
(f) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 11, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 23; or

(g) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 91, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 93.

wherein the multi-specific antibody-like protein has a N-terminus and a C-terminus, comprising in tandem from the N-terminus to the C-terminus,

a first binding domain (D1) at the N-terminus,

a second binding domain (D2) comprising a light chain moiety,

a Fc region,

a third binding domain (D3), and

a fourth binding domain (D4) at the C-terminus,

wherein the light chain moiety comprises a fifth binding domain (D5) covalently attached to the C-terminus, a sixth binding domain (D6) covalently attached to the N-terminus, or both, and

wherein the D1, D2, D3, D4, D5 and D6 each has a binding specificity to a tumor antigen, an immune signaling antigen, or a combination thereof.

7. The multi-specific antibody-like protein of claim 6, wherein D1, D2 or D6 comprises:

(a) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 1, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 13;
(b) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 3, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 15;
(c) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 5, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 17;
(d) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 7, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 19;
(e) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 9, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 21;
(f) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 11, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 23; or
(g) a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 91, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 93.

8. The multi-specific antibody-like protein of claim 6, wherein:

(a) D1 comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 7, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 19;
(b) D2 comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 91, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 93; or
(c) D6 comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 7, and a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO. 19.

9. A multi-specific monoclonal antibody, comprising the multi-specific antibody-like protein of any one of claims 6 to 8.

10. The multi-specific monoclonal antibody of claim 9, wherein the multi-specific monoclonal antibody:

(i) has a binding affinity to human CD19 with a Kd not greater than 10nM, and/or
(ii) is a humanized antibody, and/or
(iii) comprises an IgG heavy constant region.

11. The multi-specific monoclonal antibody of claim 9 or 10, comprising:

(a) a heavy chain comprising an amino acid sequence as set forth in SEQ ID NO: 67 and a light chain comprising an amino acid sequence as set forth in SEQ ID NO. 69;
(b) a heavy chain comprising an amino acid sequence as set forth in SEQ ID NO: 71 and a light chain comprising an amino acid sequence as set forth in SEQ ID NO. 73; or
(c) a heavy chain comprising an amino acid sequence as set forth in SEQ ID NO: 75 and a light chain comprising an amino acid sequence as set forth in SEQ ID NO. 77.

12. An isolated nucleic acid, encoding the amino acid sequences of the antibody or antigen binding fragment thereof, or a peptide of any one of claims 1 to 5 or the multi-specific monoclonal antibody of any one of claims 9 to 11.

13. An expression vector comprising the isolated nucleic acid of claim 12.

14. A host cell comprising the nucleic acid of claim 13, wherein the host cell is a prokaryotic cell or a eukaryotic cell.

15. A method of producing an antibody comprising culturing the host cell of claim 14 so that the antibody is produced.

16. An immune-conjugate, comprising the multi-specific monoclonal antibody of any one of claims 9 to 11 and a drug unit, wherein the drug unit is linked to the multi-specific monoclonal antibody through a linker, and 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.

17. The immune-conjugate of claim 16, wherein the drug unit comprises a cytotoxic agent, an immune regulatory reagent, or an imaging agent, or a combination thereof.

18. The immune-conjugate of claim 17, wherein:

(i) the cytotoxic agent is selected from a growth inhibitory agent or a chemotherapeutic agent from a class of tubulin binders, DNA intercalators, DNA alkylators, enzyme inhibitors, immune modulators, antimetabolite agents, or radioactive isotopes, or a combination thereof;
(ii) the cytotoxic agent is selected from a calicheamicin, camptothecin, ozogamicin, monomethyl auristatin E, emtansine, or a derivative or a combination thereof;
(iii) the immune regulatory reagents activate or suppress immune cells, T cell, NK cell, B cell, macrophage, or dendritic cell; or
(iv) the imaging agent may be radionuclide, a florescent agent, or a quantum dots, or a combination thereof.

19. A pharmaceutical composition, comprising the multi-specific monoclonal antibody of any one of claims 9 to 11 or the immune-conjugate of any one of claims 16 to 18 and a pharmaceutically acceptable carrier.

20. The pharmaceutical composition of claim 19, further comprising a chemotherapeutic agent, a growth inhibitory agent, a cytotoxic agent from class of calicheamicin, an antimitotic agent, a toxin, a radioactive isotope, or a therapeutic agent, or a combination thereof.

21. Use of a multi-specific monoclonal antibody of any one of claims 9 to 11 in the manufacture of a medicament for treating a subject with a cancer, wherein the cancer expresses CD19.

22. The use of claim 21, wherein medicament is to be co-administered with an effective amount of a therapeutic agent, wherein the therapeutic agent comprises an antibody, a chemotherapy agent, or an enzyme, or a combination thereof.

23. The use of claim 21 or 22, wherein the subject is a human.

24. A solution comprising an effective concentration of the multi-specific monoclonal antibody of any one of claims 9 to 11, wherein the solution is blood plasma obtained from a subject.