

What is Claimed is:

1. An antigen-binding protein specific for CD3, comprising:

a variable heavy chain domain comprising CDR1, CDR2 and CDR3 sequences in a human VH framework, where the CDR1 sequence has a formula:

$$G_1 \quad G_2 \quad S_3 \quad I_4 \quad X_5 \quad S_6 \quad X_7 \quad X_8 \quad X_9 \quad X_{10}$$

where X_5 , X_7 , X_8 , X_9 and X_{10} may be any amino acid;

the CDR2 sequence has the formula:

$$I_{1'} \quad X_{2'} \quad X_{3'} \quad S_{4'} \quad G_{5'} \quad X_{6'} \quad X_{7'}$$

where $X_{2'}$, $X_{3'}$, $X_{6'}$ and $X_{7'}$ may be any amino acid;

the CDR3 sequence has the formula

$$X_{1''} \quad R_{2''} \quad W_{3''} \quad R_{4''} \quad H_{5''} \quad D_{6''} \quad I_{7''} \quad X_{8''} \quad X_{9''} \quad X_{10''} \quad Y_{11''} \quad P_{12''} \quad Y_{13''} \quad Y_{14''} \quad Y_{15''} \quad Y_{16''} \quad G_{17''} \\ M_{18''} \quad D_{19''} \quad V_{20''}$$

where $X_{1''}$, $X_{8''}$, $X_{9''}$ and $X_{10''}$ may be any amino acid;

and a variable light chain domain.

2. An antigen-binding protein specific for CD3, comprising a variable heavy chain

domain comprising CDR1, CDR2 and CDR3 sequences in a human VH framework, where the CDR1, CDR2 or CDR3 are found of any of SEQ ID NO:1-68;

and a variable light chain domain.

3. An antigen-binding protein specific for CD3, comprising a variable heavy chain

domain comprising CDR1, CDR2 and CDR3 sequences in a human VH framework wherein the CDR sequences are a sequence with at least 85% identity to a CDR sequence or set of CDR sequences in any one of SEQ ID NO:1-68;

and a variable light chain domain.

4. An antigen-binding protein specific for CD3, comprising a variable heavy chain

domain comprising CDR1, CDR2 and CDR3 sequences in a human VH framework wherein the CDR sequences are a sequence with up to 3 amino acid substitutions relative to a CDR sequence or set of CDR sequences in any one of SEQ ID NO:1-68;

and a variable light chain domain.

5. The antigen-binding protein of any of claims 1-4, wherein the variable light chain domain comprises a CDR1, CDR2 and CDR3 sequences in a human VL framework wherein the CDR sequences are a sequence with up to 3 amino acid substitutions relative to a CDR sequence or set of CDR sequences in SEQ ID NO:69; or wherein the CDR sequences are a sequence with at least 85% identity to a CDR sequence or set of CDR sequences in SEQ ID NO:69.

6. The antigen-binding protein of any of claims 1-5, wherein the variable heavy chain domain comprises an amino acid sequence set forth in any of SEQ ID NO:1-68.

7. The antigen-binding protein of any of claims 1-6, wherein the variable light chain domain comprises an amino acid sequence of SEQ ID NO:69.

8. An antigen-binding protein of any of claims 1-7, wherein when contacted with T cells in an activation assays the antigen binding protein induces release of reduced levels of one or both of IL-2 and IL--10 relative to a reference anti-CD3 antibody.

9. The antigen-binding protein of any of claims 1-8, further comprising an Fc region.

10. The antigen-binding protein of claim 9, wherein the Fc region has been engineered to reduce effector functions.

11. The antigen-binding protein of any of claims 1-10, wherein the affinity (KD) of the protein for human CD3 delta epsilon is around about 10^{-6} M to around about 10^{-11} M.

12. The antigen-binding protein of any of claims 1-10, wherein the protein cross-reacts with human and Cynomolgus macaque CD3 protein.

13. The antigen-binding protein of any of claims 1-12, wherein the protein is a single chain.

14. The antigen-binding protein of any of claims 1-12, wherein the protein is two chains or a multiple thereof

15. The antigen-binding protein of any of claims 1-12, wherein the protein is three chains.

16. The antigen-binding protein of any of claims 1-12, wherein the protein is three chains and both antigen-binding arms comprise of antibody heavy and light chains

17. The antigen-binding protein of any of claims 1-12, wherein the protein further comprises a variable heavy chain domain specific for a protein other than CD3.

18. The antigen-binding protein of any of claims 1-17, wherein the protein further comprises a variable heavy chain domain specific for a protein other than CD3;

wherein when contacted with T cells in an activation assays the antigen binding protein induces release of reduced levels of one or both of IL-2 and IL-10 relative to a reference anti-CD3 antibody; and

induces more than 30% tumor cytotoxicity in standard in vitro assays using tumor cells and human T cells.

19. The antigen-binding protein of claim 17, wherein the variable heavy chain domain specific for a protein other than CD3 is a heavy chain only domain.

20. The antigen-binding protein of claim 19, wherein the variable heavy chain domain specific for a protein other than CD3 further comprises a light chain variable region.

21. The antigen-binding protein of claim 19, wherein the light chain variable region is the same as light chain variable region of the CD3-binding region.

22. The antigen-binding protein of any of claims 17-21, wherein the protein other than CD3 is a tumor associated antigen.

23. The antigen-binding protein of any of claims 17-21, wherein the protein other than CD3 is a pathogen antigen.

24. The antigen-binding protein of any of claims 17-21, wherein the protein other than CD3 is an immunoregulatory protein.

25. A pharmaceutical composition comprising an antigen-binding protein of any of claims 1-24.

26. The pharmaceutical formulation of claim 25, in a unit dose formula.

27. A polynucleotide encoding an antigen-binding protein of any of claims 1-24.

28. A vector comprising a polynucleotide of claim 27.

29. A cell comprising a vector of claim 28.

30. A method of producing an antigen-binding protein of any of claims 1-24, comprising growing a cell according to claim 29 under conditions permissive for expression of the protein, and isolating the protein from the cells.

31. A method of treatment, comprising administering to an individual an effective dose of a protein of an antigen-binding protein of any of claims 1-24.

32. The method of claim 31, wherein the individual is human.

33. A method of making an antigen-binding protein specific for CD3, comprising: immunizing OmniFlic or UniRat animals with CD3; and identifying antigen-specific heavy chain sequences.

34. A method of making an antigen-binding protein of claim 17, comprising: immunizing OmniFlic or UniRat animals with an antigen other than CD3; and identifying antigen-specific heavy chain sequences that can be combined in a molecule containing the antigen-binding protein of any of claims 1-16.

35. A bispecific antigen-binding protein, wherein the protein comprises of a binding domain specific for CD3 and a binding domain specific for an antigen other than CD3; wherein when contacted with T cells in an activation assay the bispecific antigen binding protein induces release of reduced levels of one or both of IL-2 and IL-10 relative to a reference anti-CD3 antibody; and

induces more than 30% tumor cytotoxicity in standard in vitro assays using tumor cells and human T cells.

36. A bispecific antibody comprising:

(i) a CD3-binding variable region comprising CDR1, CDR2 and CDR3 sequences of SEQ ID NO:1 in a human VH framework;

(ii) a variable light chain domain comprising CDR1, CDR2 and CDR3 sequences of SEQ ID NO:69 in a human VL framework;

(iii) a single chain anti-BCMA variable region comprising CDR1, CDR2 and CDR3 sequences at positions 26-33; 51-58; 97-108, respectively, of SEQ ID NO:70 in single or in tandem configuration.

37. The bispecific antibody of claim 36, further comprising an Fc region.

38. The bispecific antibody of claim 37, wherein the CD3-binding variable region comprises SEQ ID NO:1, the light chain variable region comprises SEQ ID NO:69 and the BCMA-binding variable region comprises SEQ ID NO:70 or SEQ ID NO:71.