

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:

$$G_1 \quad F_2 \quad T_3 \quad F_4 \quad X_5 \quad X_6 \quad Y_7 \quad A_8$$

where X_5 , X_6 may be any amino acid;

the CDR2 sequence has the formula:

$$I_1' \quad S_2' \quad W_3' \quad N_4' \quad S_5' \quad G_6' \quad S_7' \quad I_8'$$

the CDR3 sequence has the formula

$$A_1'' \quad K_2'' \quad D_3'' \quad S_4'' \quad R_5'' \quad G_6'' \quad Y_7'' \quad G_8'' \quad X_9'' \quad Y_{10}'' \quad X_{11}'' \quad X_{12}'' \quad G_{13}'' \quad G_{12}'' \quad A_{15}'' \quad Y_{16}''$$

where X_9'' , X_{11}'' , X_{12}'' may be any amino acid:

and a variable light chain domains.

2. The antigen-binding protein of claim 1, 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:1-18;

and a variable light chain domain.

3. The antigen-binding protein of claim 1, 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:1-18;

and a variable light chain domain.

4. The antigen-binding protein of claim 1, 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:1-78 or SEQ ID NO:80-102;

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:19; 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:19.

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:1-18.

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:19.

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 IL6 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 1-11, wherein the protein is a single chain.

13. The antigen-binding protein of any of claims 1-11, wherein the protein is two chains or a multiple thereof

14. The antigen-binding protein of any of claims 1-11, wherein the protein is three chains.

15. The antigen-binding protein of any of claims 1-11, wherein the protein is three chains and both antigen-binding arms comprise of antibody heavy and light chains

16. The antigen-binding protein of any of claims 1-11, wherein the protein further comprises a variable heavy chain domain specific for a protein other than CD3.

17. The antigen-binding protein of any of claims 1-16, 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 IL6 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.

18. The antigen-binding protein of claim 16, wherein the variable heavy chain domain specific for a protein other than CD3 is a heavy chain only domain.

19. The antigen-binding protein of claim 16, wherein the variable heavy chain domain specific for a protein other than CD3 further comprises a light chain variable region.

20. The antigen-binding protein of claim 16, wherein the light chain variable region is the same as light chain variable region of the CD3-binding region.

21. The antigen-binding protein of any of claims 16-20, wherein the protein other than CD3 is a tumor associated antigen.

22. The antigen-binding protein of any of claims 16-20, wherein the protein other than CD3 is a pathogen antigen.

23. The antigen-binding protein of any of claims 16-20, wherein the protein other than CD3 is an immunoregulatory protein.

24. A pharmaceutical composition comprising an antigen-binding protein of any of claims 1-23.

25. The pharmaceutical formulation of claim 24, in a unit dose formula.

26. A polynucleotide encoding an antigen-binding protein of any of claims 1-23.

27. A vector comprising a polynucleotide of claim 26.

28. A cell comprising a vector of claim 27.

29. 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.

30. A method of treatment, comprising administering to an individual an effective dose of a protein of an antigen-binding protein of any of claims 1-23.

31. The method of claim 30, wherein the individual is human.

32. A method of making an antigen-binding protein that specifically binds to CD3, comprising:

immunizing OmniFlic or UniRat animals with CD3; and
identifying antigen-specific heavy chain sequences.

33. A method of making an antigen-binding protein of claim 16, 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 1-15.

34. 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.

35. 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:19 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:20 in single or in tandem configuration.

36. The bispecific antibody of claim 35, further comprising an Fc region.

37. The bispecific antibody of claim 35, wherein the CD3-binding variable region comprises SEQ ID NO:1, the light chain variable region comprises SEQ ID NO:19 and the BCMA-binding variable region comprises SEQ ID NO:20 or SEQ ID NO:21.