

WHAT IS CLAIMED IS:

1. An isolated monoclonal antigen-binding protein that binds to CD3, wherein the isolated monoclonal antibody binds an epitope on CD3 comprising at least one residue selected from CD3 epsilon (SEQ ID NO:23): K73 and S83; and CD3 delta (SEQ ID NO:24) K82 and C93.
2. The antigen-binding protein of claim 1, wherein the epitope on CD3 comprises the region of CD3 delta defined by K82, E83, S84, T85, V86, Q87, V88, H89, Y90, R91, M92, C93.
3. The antigen-binding protein of claim 1, wherein the epitope on CD3 comprises the region of CD3 epsilon defined by K73, N74, I75, G76, S77, D78, E79, D80, H81, L82, S83.
4. The antigen-binding protein of any of claims 1-3, wherein the epitope comprises a conformational epitope with residues of both CD3 delta and CD3 epsilon.
5. The antigen-binding protein of any of claims 1-4, wherein the conformational epitope comprises each of residues CD3 ϵ K73 and S83; CD3 δ K82 and C93.
6. The antigen-binding protein of any of claims 1-5, wherein the antibody does not cross-react with cynomolgus CD3 protein.
7. The antigen-binding protein of any of claims 1-6, wherein the antigen-binding protein induces a cytokine release upon binding to a T cell that is not more than about 200% of the maximum cytokine release observed with F2B antibody.
8. The antigen-binding protein of any of claims 1-7, wherein the binding affinity for CD3 is 50 nM or greater.
9. The isolated monoclonal antigen-binding protein of any of claims 1-8, wherein the isolated monoclonal antigen-binding protein is a human antibody.
10. The isolated monoclonal antigen-binding protein of any of claims 1-8, wherein the isolated monoclonal antigen-binding protein is a humanized antibody.
11. The antigen-binding protein of any of claims 1-10, wherein the variable region of the light chain comprises a set of CDR sequences in SEQ ID NO:19.

12. The antigen-binding protein of any of claims 1-11, wherein the variable light chain domain comprises an amino acid sequence of SEQ ID NO:19.

13. The antigen-binding protein of any of claims 1-12, wherein the antibody comprises a set of CDR sequences other than those set forth in SEQ ID NO:1-18.

14. The antigen-binding protein of any of claims 1-13, further comprising an Fc region.

15. The antigen-binding protein of claim 14, wherein the Fc region has been engineered to reduce effector functions.

16. The antigen-binding protein of any of claims 1-15, wherein the protein is a single chain.

17. The antigen-binding protein of any of claims 1-15, wherein the protein is two chains or a multiple thereof

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

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

20. The antigen-binding protein of any of claims 1-15, wherein the protein further comprises a variable heavy chain domain specific for a protein other than CD3.

21. The antigen-binding protein of any of claims 1-20, 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.

22. The antigen-binding protein of claim 21, wherein the variable heavy chain domain specific for a protein other than CD3 is a heavy chain only domain.

23. The antigen-binding protein of claim 21, wherein the variable heavy chain domain specific for a protein other than CD3 further comprises a light chain variable region.
24. The antigen-binding protein of claim 21, wherein the light chain variable region is the same as light chain variable region of the CD3-binding region.
25. The antigen-binding protein of any of claims 21-24 wherein the protein other than CD3 is a tumor associated antigen.
26. The antigen-binding protein of any of claims 21-24, wherein the protein other than CD3 is a pathogen antigen.
27. The antigen-binding protein of any of claims 21-24, wherein the protein other than CD3 is an immunoregulatory protein.
28. A pharmaceutical composition comprising an antigen-binding protein of any of claims 1-27.
29. The pharmaceutical composition of claim 28, in a unit dose formula.
30. A polynucleotide encoding an antigen-binding protein of any one of claims 1-27.
31. A vector comprising the polynucleotide of claim 30.
32. A cell comprising the vector of claim 31.
33. A method of producing an antigen-binding protein of any one of claims 1-27, comprising growing a cell according to claim 32 under conditions permissive for expression of the protein, and isolating the protein from the cell and/or a cell culture medium.
34. A method of treatment, comprising administering to an individual an effective dose of an antigen-binding protein of any one of claims 1-27, or the pharmaceutical composition of claim 28.
35. Use of an antigen-binding protein of any one of claims 1-27 in the preparation of a medicament for the treatment of a disease.

36. An antigen-binding protein of any one of claims 1-27 for use in the treatment of a disease.
37. The method or use of any one of claims 34-36, wherein the individual is human.