

WHAT IS CLAIMED:

1. A chimeric autoantibody receptor (CAAR) comprising:
 - (a) an extracellular proteinase 3 (PR3) antibody binding domain, wherein the PR3 antibody binding domain is a mutant PR3 protein that has reduced enzymatic activity compared with a wild type PR3 protein having the sequence set forth in SEQ ID NO:1;
 - (b) a transmembrane region; and
 - (c) an intracellular signaling region.
2. The CAAR of claim 1, further comprising a spacer between the extracellular PR3 antibody binding domain and the transmembrane domain.
3. The CAAR of claim 1 or claim 2, wherein the mutant PR3 protein comprises an amino acid substitution, wherein the amino acid substitution is selected from the group consisting of G4P, H44A, D91N, D175N, S176A and S176C; or the amino acid substitution is a conservative substitution of an amino acid substitution selected from the group consisting of G4P, H44A, D91N, D175N, S176A and S176C.
4. The CAAR of any one of claims 1-3, wherein the mutant PR3 protein comprises the amino acid substitution G4P.
5. The CAAR of any one of claims 1-4, wherein the PR3 antibody binding domain comprises a sequence of amino acids that exhibits at least 90% sequence identity to SEQ ID NO:9.
6. The CAAR of any one of claims 1-5, wherein the PR3 antibody binding domain comprises the sequence of amino acids set forth in SEQ ID NO:9.
7. The CAAR of any one of claims 1-3, wherein the mutant PR3 protein comprises the amino acid substitution H44A.

8. The CAAR of any one of claims 1-3 and claim 7, wherein the PR3 antibody binding domain comprises a sequence of amino acids that exhibits at least 90% sequence identity to SEQ ID NO:10.

9. The CAAR of any one of claims 1-3, 7, and 8, wherein the PR3 antibody binding domain comprises the sequence of amino acids set forth in SEQ ID NO:10.

10. The CAAR of any one of claims 1-9, wherein the transmembrane region is or comprises a transmembrane domain from CD4, CD28, or CD8.

11. The CAAR of any one of claims 1-10, wherein the transmembrane region is or comprises a transmembrane domain from CD28.

12. The CAAR of any one of claims 1-11, wherein the transmembrane region is or comprises SEQ ID NO: 26 or an amino acid sequence having at least at or about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO:26.

13. The CAAR of any one of claims 1-10, wherein the transmembrane region is or comprises a transmembrane domain from CD8.

14. The CAAR of any one of claims 1-10 and 13, wherein the transmembrane region is or comprises SEQ ID NO: 98 or an amino acid sequence having at least at or about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO:98.

15. The CAAR of any one of claims 1-14, wherein the intracellular signaling region comprises an intracellular signaling domain capable of inducing a primary activation signal in a T cell.

16. The CAAR of claim 15, wherein the intracellular signaling domain is a cytoplasmic signaling domain of a CD3-zeta (CD3ζ) chain.

17. The CAAR of claim 15 or claim 16, wherein the intracellular signaling domain comprises the sequence set forth in SEQ ID NO:28, or an amino acid sequence having at least at or about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO:28.

18. The CAAR of any one of claims 15-17, wherein the intracellular signaling region further comprises a costimulatory signaling region.

19. The CAAR of claim 18, wherein the costimulatory signaling region comprises an intracellular signaling domain of CD28, 4-1BB, or ICOS.

20. The CAAR of claim 18 or claim 19, wherein the costimulatory signaling region comprises an intracellular signaling domain of 4-1BB.

21. The CAAR of any one of claims 18-20, wherein the costimulatory signaling region comprises the sequence set forth in SEQ ID NO:27 or an amino acid sequence having at least at or about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO: 27.

22. The CAAR of any one of claims 2-21, wherein the spacer comprises at least a portion of an immunoglobulin or a variant thereof.

23. The CAAR of any one of claims 2-22, wherein the spacer comprises:

- (i) a hinge region of an immunoglobulin or a variant thereof;
- (ii) an IgG4 hinge region or a variant thereof;
- (iii) a variant IgG4 hinge region comprising substitution of amino acids CPSC to CPPC compared to the wild-type IgG4 hinge region;
- (iv) between 12 and 15 amino acids;
- (v) the sequence set forth in SEQ ID NO: 22 or SEQ ID NO:23;
- (vi) a hinge region of an immunoglobulin and a CH3 region of an immunoglobulin; or
- (vii) a hinge region of an immunoglobulin, a CH2 region of an immunoglobulin or a chimeric CH2 region of two different immunoglobulins, and a CH3 region of an immunoglobulin.

24. The CAAR of any one of claims 2-21, wherein the spacer comprises amino acids GGGGS (SEQ ID NO:99).

25. The CAAR of any one of claims 2-21 and 24, wherein the spacer is set forth in SEQ ID NO: 99.

26. The CAAR of any one of claims 2-21 and 24, wherein the spacer is set forth in SEQ ID NO: 100.

27. The CAAR of any one of claims 1-26, wherein the CAAR comprises a sequence of amino acids that exhibits at least 85% sequence identity to the sequence set forth in any of SEQ ID NOS: 29, 30, 31, 38, 39, 40, 53, 54, 55, 56, 57, 58, 104, 110, or 111.

28. A CAAR comprising:

(a) a PR3 antibody binding domain comprising the sequence set forth in SEQ ID NO:9;

(b) a spacer comprising the sequence set forth in SEQ ID NO:100;

(c) a transmembrane region comprising the sequence set forth in SEQ ID NO:26;

(d) a costimulatory signaling region comprising the sequence set forth in SEQ ID NO:27; and

(e) an intracellular signaling region comprising the sequence set forth in SEQ ID NO:28.

29. A CAAR comprising a sequence of amino acids that exhibits at least 90% sequence identity to SEQ ID NO:104 wherein the sequence of amino acids comprises a G4P mutation with reference to the numbering of positions in SEQ ID NO:1.

30. A CAAR comprising:

(a) a PR3 antibody binding domain comprising the sequence set forth in SEQ ID NO:9;

(b) a spacer comprising the sequence set forth in SEQ ID NO:22;

(c) a transmembrane region comprising the sequence set forth in SEQ ID NO:98;

(d) a costimulatory signaling region comprising the sequence set forth in SEQ ID NO:27; and

(e) an intracellular signaling region comprising the sequence set forth in SEQ ID NO:28.

31. A CAAR comprising a sequence of amino acids that exhibits at least 90% sequence identity to SEQ ID NO:110 wherein the sequence of amino acids comprises a G4P mutation with reference to the numbering of positions in SEQ ID NO:1.

32. A CAAR comprising:

(a) a PR3 antibody binding domain comprising the sequence set forth in SEQ ID NO:10;

(b) a spacer comprising the sequence set forth in SEQ ID NO:100;

(c) a transmembrane region comprising the sequence set forth in SEQ ID NO:98;

(d) a costimulatory signaling region comprising the sequence set forth in SEQ ID NO:27; and

(e) an intracellular signaling region comprising the sequence set forth in SEQ ID NO:28.

33. A CAAR comprising a sequence of amino acids that exhibits at least 90% sequence identity to SEQ ID NO:111 or 119 wherein the sequence of amino acids comprises a H44A mutation with reference to the numbering of positions in in SEQ ID NO:1.

34. The CAAR of any one of claims 1-33, wherein the CAAR is able to be specifically bound by an anti-PR3 antineutrophil cytoplasmic antibody (PR3-ANCA); and/or the CAAR is specific for PR3-reactive B cells.

35. A polynucleotide comprising a nucleic acid encoding the CAAR of any one of claims 1-34.

36. A vector, comprising the polynucleotide of claim 35.

37. A cell comprising the CAAR of any one of claims 1-34, the polynucleotide of claim 35, or the vector of claim 36.

38. The cell of claim 37, that is a lymphocyte.
39. The cell of claim 37 or 38, wherein the cell is a T cell and the T cell is a CD4+ T cell or a CD8+ T cell.
40. A composition comprising the cell of any one of claims 37-39.
41. A method of killing PR3-reactive B cells, the method comprising contacting a PR3-reactive B cell with the cell of any one of claims 37-39 or the composition of claim 40, wherein the method is performed *in vitro* or *ex vivo*.
42. A composition comprising the cell of any one of claims 37-39 or the composition of claim 40 for use in treating a disease or disorder in a subject.
43. Use of a composition comprising the cell of any one of claims 37-39 or the composition of claim 40 in the manufacture of a medicament for treating a disease or disorder in a subject, wherein the disease or disorder is an autoimmune condition.
44. The use of claim 43, wherein the disease or disorder is antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), optionally wherein the AAV is PR3-AAV.
45. The use of claim 43 or claim 44, wherein the disease or disorder is selected from the group consisting of granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), or eosinophilic granulomatosis with polyangiitis (EGPA).
46. Use of a composition comprising the cell of any one of claims 37-39 or the composition of claim 40 in the manufacture of a medicament for treating PR3-ANCA vasculitis in a subject, wherein the subject has received a remission induction therapy or a preconditioning therapy that has been shown to be effective to deplete ANCAs.
47. The use of claim 46, wherein the remission induction therapy comprises cyclophosphamide.