CLAIMS

WHAT IS CLAIMED:

1. A composition for use for treating a subject having systemic autoimmune disease,

wherein the composition comprises a dose of CD19-directed genetically modified T cells,

wherein the T cells of the dose are positive for expression of a chimeric antigen receptor (CAR) that binds CD19 and the dose is from 1×10^6 to 50×10^6 CAR-positive viable T cells, and

wherein the composition is for administration to a subject having or suspected of having a moderate or severe systemic autoimmune disease.

2. Use of a composition in the manufacture of a medicament for treating systemic autoimmune disease,

wherein the composition comprises a dose of CD19-directed genetically modified T cells,

wherein the T cells of the dose are positive for expression of a chimeric antigen receptor (CAR) that binds CD19 and the dose is from 1×10^6 to 50×10^6 CAR-positive viable T cells, and

wherein the composition is for administration to a subject having or suspected of having a moderate or severe systemic autoimmune disease.

3. The composition for use of claim 1 or the use of claim 2, wherein the systemic autoimmune disease is selected from the group consisting of systemic lupus erythematosus (SLE), lupus nephritis, multiple sclerosis (MS), autoimmune vasculitis, demyelinating polyradiculoneuropathy, bullous pemphigoid, Sjogren's syndrome, progressive systemic sclerosis (i.e., scleroderma), myositis, idiopathic inflammatory myositis (IIM), including dermatomyositis, polymyositis and necrotizing myositis, mixed connective tissue disorder (MCTD), highly active relapsing-remitting multiple sclerosis, primary progressive MS, ANCA-associated vasculitis (AAV), Crohn’s disease, myasthenia gravis, Behçet’s, rheumatoid arthritis, IgA nephropathy, pemphigus vulgaris, autoimmune hemolytic anemia, immune thrombocytopenia, IgG4-related diseases, membranous nephropathy, cutaneous lupus erythematosus, sarcoidosis, light chain amyloidosis, acute respiratory distress syndrome, atopic eczema, hereditary angioedema, hidradenitis suppurativa, inclusion-body myositis, inflammatory bowel disease, mastocytosis,

multifocal motor neuropathy, necrotizing myopathy, neuromyelitis optica spectrum disorder, POEMS syndrome, primary biliary cholangitis, psoriasis, rhesus hemolytic disease, Still's disease, type 1 diabetes, urticaria, capillary leakage syndrome, cytokine release syndrome, erythema multiforme, pyoderma gangrenosum, x-linked agammaglobulinemia, antiphospholipid syndrome, and chronic inflammatory demyelinating polyneuropathy.

4. A composition for use for treating a subject having severe systemic lupus erythematosus (SLE) or reducing SLE disease activity,

wherein the composition comprises a dose of CD19-directed genetically modified T cells,

wherein the T cells of the dose are positive for expression of a chimeric antigen receptor (CAR) that binds CD19 and the dose is from 1×10^6 to 50×10^6 CAR-positive viable T cells, and

wherein the composition is for administration to a subject having or suspected of having severe SLE.

5. Use of a composition in the manufacture of a medicament for treating severe systemic lupus erythematosus (SLE) or reducing SLE disease activity,

wherein the composition comprises a dose of CD19-directed genetically modified T cells,

wherein the T cells of the dose are positive for expression of a chimeric antigen receptor (CAR) that binds CD19 and the dose is from 1×10^6 to 50×10^6 CAR-positive viable T cells, and

wherein the composition is for administration to a subject having or suspected of having severe SLE.

6. A composition for use for treating a subject having lupus nephritis,

wherein the composition comprises a dose of CD19-directed genetically modified T cells,

wherein the T cells of the dose are positive for expression of a chimeric antigen receptor (CAR) that binds CD19 and the dose is from 1×10^6 to 50×10^6 CAR-positive viable T cells, and

wherein the composition is for administration to a subject having or suspected of having lupus nephritis.

7. Use of a composition in the manufacture of a medicament for treating lupus nephritis,

wherein the composition comprises a dose of CD19-directed genetically modified T cells,

wherein the T cells of the dose are positive for expression of a chimeric antigen receptor (CAR) that binds CD19 and the dose is from 1×10^6 to 50×10^6 CAR-positive viable T cells, and

wherein the composition is for administration to a subject having or suspected of having lupus nephritis.

8. The composition for use of claim 4 or claim 6 or the use of claim 5 or claim 7, wherein the subject does not have drug-induced SLE, clinically significant CNS pathology, related systemic autoimmune diseases, and/or SLE overlap syndromes.

9. The composition for use or the use of any of the preceding claims, wherein the composition is capable of reducing the systemic autoimmune disease activity in the subject or reducing SLE disease activity in the subject.

10. A composition for use for treating a subject having idiopathic inflammatory myopathy (IIM) or reducing IIM disease activity,

wherein the composition comprises a dose of CD19-directed genetically modified T cells,

wherein the T cells of the dose are positive for expression of a chimeric antigen receptor (CAR) that binds CD19 and the dose is from 1×10^6 to 50×10^6 CAR-positive viable T cells, and

wherein the composition is for administration to a subject having or suspected of having IIM.

11. Use of a composition in the manufacture of a medicament for treating idiopathic inflammatory myopathy (IIM) or reducing IIM disease activity,

wherein the composition comprises a dose of CD19-directed genetically modified T cells,

wherein the T cells of the dose are positive for expression of a chimeric antigen receptor (CAR) that binds CD19 and the dose is from 1×10^6 to 50×10^6 CAR-positive viable T cells, and

wherein the composition is for administration to a subject having or suspected of having IIM.

12. A composition for use for treating a subject having systemic sclerosis (SSc) or reducing SSc disease activity,

wherein the composition comprises a dose of CD19-directed genetically modified T cells,

wherein the T cells of the dose are positive for expression of a chimeric antigen receptor (CAR) that binds CD19 and the dose is from 1×10^6 to 50×10^6 CAR-positive viable T cells, and

wherein the composition is for administration to a subject having or suspected of having SSc.

13. Use of a composition in the manufacture of a medicament for treating systemic sclerosis (SSc) or reducing SSc disease activity,

wherein the composition comprises a dose of CD19-directed genetically modified T cells,

wherein the T cells of the dose are positive for expression of a chimeric antigen receptor (CAR) that binds CD19 and the dose is from 1×10^6 to 50×10^6 CAR-positive viable T cells, and

wherein the composition is for administration to a subject having or suspected of having SSc.

14. A composition for use for treating a subject having multiple sclerosis (MS) or reducing MS disease activity,

wherein the composition comprises a dose of CD19-directed genetically modified T cells,

wherein the T cells of the dose are positive for expression of a chimeric antigen receptor (CAR) that binds CD19 and the dose is from 1×10^6 to 50×10^6 CAR-positive viable T cells, and

wherein the composition is for administration to a subject having or suspected of having MS.

15. Use of a composition in the manufacture of a medicament for treating multiple sclerosis (MS) or reducing MS disease activity,

wherein the composition comprises a dose of CD19-directed genetically modified T cells,

wherein the T cells of the dose are positive for expression of a chimeric antigen receptor (CAR) that binds CD19 and the dose is from 1×10^6 to 50×10^6 CAR-positive viable T cells, and

wherein the composition is for administration to a subject having or suspected of having MS.

16. The composition for use or the use of any of the preceding claims, wherein the subject is refractory to treatment with one or more prior therapies for the disease.

17. The composition for use or the use of any of the preceding claims, wherein the composition is capable of reducing the autoimmune disease activity in the subject and/or wherein reducing disease activity in the subject comprises reduced inflammation in the subject.

18. A composition for use for treating a subject having autoimmune vasculitis (AAV) or reducing AAV activity,

wherein the composition comprises a dose of CD19-directed genetically modified T cells,

wherein the T cells of the dose are positive for expression of a chimeric antigen receptor (CAR) that binds CD19 and the dose is from 1×10^6 to 50×10^6 CAR-positive viable T cells, and

wherein the composition is for administration to a subject having or suspected of having AAV.

19. Use of a composition in the manufacture of a medicament for treating autoimmune vasculitis (AAV) or reducing AAV activity,

wherein the composition comprises a dose of CD19-directed genetically modified T cells,

wherein the T cells of the dose are positive for expression of a chimeric antigen receptor (CAR) that binds CD19 and the dose is from 1×10^6 to 50×10^6 CAR-positive viable T cells, and

wherein the composition is for administration to a subject having or suspected of having AAV.

20. A composition for use for treating a subject having IgA nephropathy or reducing IgA nephropathy disease activity,

wherein the composition comprises a dose of CD19-directed genetically modified T cells,

wherein the T cells of the dose are positive for expression of a chimeric antigen receptor (CAR) that binds CD19 and the dose is from 1×10^6 to 50×10^6 CAR-positive viable T cells, and

wherein the composition is for administration to a subject having or suspected of having IgA nephropathy.

21. Use of a composition in the manufacture of a medicament for treating IgA nephropathy or reducing IgA nephropathy disease activity,

wherein the composition comprises a dose of CD19-directed genetically modified T cells,

wherein the T cells of the dose are positive for expression of a chimeric antigen receptor (CAR) that binds CD19 and the dose is from 1×10^6 to 50×10^6 CAR-positive viable T cells, and

wherein the composition is for administration to a subject having or suspected of having IgA nephropathy.

22. A composition for use for treating a subject having pemphigus vulgaris or reducing pemphigus vulgaris disease activity,

wherein the composition comprises a dose of CD19-directed genetically modified T cells,

wherein the T cells of the dose are positive for expression of a chimeric antigen receptor (CAR) that binds CD19 and the dose is from 1×10^6 to 50×10^6 CAR-positive viable T cells, and

wherein the composition is for administration to a subject having or suspected of having pemphigus vulgaris.

23. Use of a composition in the manufacture of a medicament for treating pemphigus vulgaris or reducing pemphigus vulgaris disease activity,

wherein the composition comprises a dose of CD19-directed genetically modified T cells,

wherein the T cells of the dose are positive for expression of a chimeric antigen receptor (CAR) that binds CD19 and the dose is from 1×10^6 to 50×10^6 CAR-positive viable T cells, and

wherein the composition is for administration to a subject having or suspected of having pemphigus vulgaris.

24. A composition for use for treating a subject having myasthenia gravis or reducing myasthenia gravis disease activity,

wherein the composition comprises a dose of CD19-directed genetically modified T cells,

wherein the T cells of the dose are positive for expression of a chimeric antigen receptor (CAR) that binds CD19 and the dose is from 1×10^6 to 50×10^6 CAR-positive viable T cells, and

wherein the composition is for administration to a subject having or suspected of having myasthenia gravis.

25. Use of a composition in the manufacture of a medicament for treating myasthenia gravis or reducing myasthenia gravis disease activity,

wherein the composition comprises a dose of CD19-directed genetically modified T cells,

wherein the T cells of the dose are positive for expression of a chimeric antigen receptor (CAR) that binds CD19 and the dose is from 1×10^6 to 50×10^6 CAR-positive viable T cells, and

wherein the composition is for administration to a subject having or suspected of having myasthenia gravis.

26. The composition for use or the use of any of the preceding claims, wherein the T cells are autologous to the subject, or

a leukapheresis sample is obtained from the subject for manufacturing the composition comprising engineered T cells.

27. The composition for use or the use of any of the preceding claims, wherein prior to the administration, the subject has been preconditioned with a lymphodepleting therapy; and/or

immediately prior to the administration of the dose of CD19-directed genetically modified T cells to the subject, a lymphodepleting therapy is to be administered to the subject, wherein the lymphodepleting therapy comprises the administration of fludarabine and/or cyclophosphamide.

28. The composition for use or the use of any of the preceding claims, wherein the CAR comprises an extracellular antigen-binding domain that binds CD19, a transmembrane domain, and an intracellular signaling domain,

optionally wherein the CAR comprises a hinge spacer between the extracellular antigen-binding domain and the transmembrane domain, further optionally wherein the hinge spacer is an immunoglobulin hinge or a CD8a hinge.

29. The composition for use or the use of claim 28, wherein:

(a)

(i) the extracellular antigen-binding domain is an FMC63 monoclonal antibody-derived single chain variable fragment (scFv);

(ii) the extracellular antigen-binding domain comprises a variable heavy chain set forth in SEQ ID NO:41 and a variable light chain set forth in SEQ ID NO:42; and/or

(iii) the scFv is set forth as SEQ ID NO: 43;

(b) the transmembrane domain is a transmembrane domain from CD28; and/or

(c) the intracellular signaling domain comprises a 4-1BB costimulatory domain and a CD3-zeta activation domain.

30. The composition for use or the use of any one of the preceding claims, wherein the CAR is a monospecific CAR directed to CD19, or

the CAR is a tandem bispecific CAR directed against CD19 and at least one other antigen expressed on B cells.

31. The composition for use or the use of any of the preceding claims, wherein the CAR comprises, in order from N- to C-terminus, an FMC63 monoclonal antibody-derived single chain variable fragment (scFv), IgG4 hinge region, a CD28 transmembrane domain, a 4-1BB (CD137) costimulatory domain, and a CD3-zeta signaling domain.

32. The composition for use or the use of any of the preceding claims, wherein:

the CAR contains in order from N-terminus to C-terminus: an extracellular antigen-binding domain that is the scFv set forth in SEQ ID NO: 43, the spacer set forth in SEQ ID NO:1, the transmembrane domain set forth in SEQ ID NO:8, the 4-1BB costimulatory signaling domain set forth in SEQ ID NO:12, and the signaling domain of a CD3-zeta (CD3ζ) chain set forth in SEQ ID NO:13; and/or

the CAR comprises the amino acid sequence set forth in SEQ ID NO:59 or a sequence having at least 85% sequence identity thereto.

33. The composition for use or the use of any of the preceding claims, wherein:

the dose of T cells comprises $CD4^+$ T cells expressing the CAR and $CD8^+$ T cells expressing the CAR;

the dose of T cells comprises $CD4^+$ T cells expressing the CAR and $CD8^+$ T cells expressing the CAR at a ratio between about 1:5 and about 5:1; and/or

at least or at least about 90% of the cells in the composition are $CD3^+$ cells and/or wherein at least 25% of the T cells in the composition are CAR+ T cells.

34. The composition for use or the use of any of the preceding claims, wherein:

a) between at or about 5% and at or about 30% of the CAR^+ T cells in the composition express a marker of apoptosis; or

b) less than 10% of the T cells in the composition express a marker of apoptosis.

35. The composition for use or the use of any of the preceding claims, wherein one or more of:

a) at least or at least about 80% of the CAR^+ T cells in the composition are of a naïve-like or central memory phenotype;

b) at least or at least about 80% of the CAR^+ T cells in the composition are of a naïve-like or central memory phenotype, and the marker expressed on naïve-like or central memory T cells is selected from the group consisting of CD45RA, CD27, CD28, and CCR7;

c) at least 85% of the CAR+ T cells in the composition are CCR7+;

d) at least 85% of the CD8+CAR+ T cells in the composition are CCR7+ and at least 90% of the CD4+ CAR+ T cells in the composition are CCR7+;

e) at least or at least about 80% of the CAR^+ T cells in the composition that are of a naïve-like or central memory phenotype have a phenotype selected from one or more of phenotypes $CCR7^+CD45RA^+$, CCR7+$CD45RA^-$, $CD27^+CCR7^+$, or $CD62L^-CCR7^+$;

f) at least 40% of the CAR+ T cells are CD45RA+CCR7+;

g) at least 20% of the CAR+ T cells are CD45RA-CCR7+;

h) at least about 50% of CD4+CAR+ T cells in the composition are CCR7+$CD45RA^-$; and/or

i) at least about 30% of CD8+CAR+ T cells in the composition are CCR7+$CD45RA^-$.

36. The composition for use or the use of any of the preceding claims, wherein the composition comprises:

(a)

(i) at least 60% of the T cells in the composition are viable;

(ii) at least 25% of the T cells of the composition are CAR+ T cells;

(iii) at least 85% of the CD8+CAR+ T cells in the composition are CCR7+; and

(iv) at least 90% of the CD4+ CAR+ T cells in the composition are CCR7+;

(b)

(i) at least 60% of the T cells in the composition are viable,

(ii) at least 25% of the T cells of the composition are CAR+; and

(iii) greater than at or about 40% of the CAR+ T cells in the composition are CCR7+CD45RA+; or

(c)

(i) at least 60% of the T cells in the composition are viable;

(ii) at least 25% of the T cells of the composition are CAR+; and

(iii) greater than 20% of the CAR+ T cells in the composition are CCR7+CD45RA-.

37. An ex vivo process for manufacturing a composition comprising CD19-directed genetically modified human T cells, the process comprising:

(i) stimulating an input composition comprising primary T cells obtained from a subject that has a severe or moderate systemic autoimmune disease by contacting the primary T cells with a stimulatory reagent comprising an anti-CD3 antibody or antigen-binding fragment thereof and an anti-CD28 antibody or antigen-binding fragment thereof;

(ii) introducing into T cells of the stimulated population a heterologous polynucleotide encoding a CAR, thereby generating a population of engineered T cells;

(iii) incubating the population of engineered T cells, thereby generating an incubated population of engineered T cells, wherein the heterologous polynucleotide becomes integrated into the genome of T cells of the incubated population;

(iv) harvesting T cells of the incubated population of engineered T cells to obtain a population of CD19-directed CAR engineered T cells autologous to the subject that has the severe or moderate systemic autoimmune disease; and

(v) formulating the population of CD19-directed engineered T cells in a composition to produce a formulated composition, wherein the formulated composition comprises one or more unit doses, wherein the unit dose is from 1×10^6 to 50×10^6 CAR-positive viable T cells.

38. The ex vivo process of claim 37, wherein the systemic autoimmune disease is selected from the group consisting of lupus nephritis, multiple sclerosis (MS), autoimmune vasculitis, demyelinating polyradiculoneuropathy, bullous pemphigoid, systemic lupus erythematosus (SLE), Sjogren's syndrome, progressive systemic sclerosis (SSc) (i.e., scleroderma), myositis, idiopathic inflammatory myositis (IIM), including dermatomyositis,

polymyositis and necrotizing myositis, mixed connective tissue disorder (MCTD), highly active relapsing-remitting multiple sclerosis, primary progressive MS, ANCA-associated vasculitis (AAV), Crohn's disease, Behçet's, rheumatoid arthritis, IgA nephropathy, pemphigus vulgaris, myasthenia gravis, autoimmune hemolytic anemia, immune thrombocytopenia, IgG4-related diseases, membranous nephropathy, cutaneous lupus erythematosus, sarcoidosis, light chain amyloidosis, acute respiratory distress syndrome, atopic eczema, hereditary angioedema, hidradenitis suppurativa, inclusion-body myositis, inflammatory bowel disease, mastocytosis, multifocal motor neuropathy, necrotizing myopathy, neuromyelitis optica spectrum disorder, POEMS syndrome, primary biliary cholangitis, psoriasis, rhesus hemolytic disease, Still's disease, type 1 diabetes, urticaria, capillary leakage syndrome, cytokine release syndrome, erythema multiforme, pyoderma gangrenosum, x-linked agammaglobulinemia, antiphospholipid syndrome, and chronic inflammatory demyelinating polyneuropathy.

39. The ex vivo process of claim 37 or claim 38, wherein one or more of:

a) at least about 80% of the CAR^+ T cells in the composition are of a naïve-like or central memory phenotype;

b) at least or at least about 80% of the CAR^+ T cells in the composition are of a naïve-like or central memory phenotype, and the marker expressed on naïve-like or central memory T cells is selected from the group consisting of CD45RA, CD27, CD28, and CCR7;

c) at least 85% of the CAR+ T cells in the composition are CCR7+;

d) at least 85% of the CD8+CAR+ T cells in the composition are CCR7+ and at least 90% of the CD4+ CAR+ T cells in the composition are CCR7+;

e) at least or at least about 80% of the CAR^+ T cells in the composition that are of a naïve-like or central memory phenotype have a phenotype selected from one or more of phenotypes $CCR7^+CD45RA^+$, CCR7+$CD45RA^-$, $CD27^+CCR7^+$, or $CD62L^-CCR7^+$;

f) at least 40% of the CAR+ T cells are CD45RA+CCR7+;

g) at least 20% of the CAR+ T cells are CD45RA-CCR7+;

h) at least about 50% of CD4+CAR+ T cells in the composition are CCR7+$CD45RA^-$; and/or

i) at least about 30% of CD8+CAR+ T cells in the composition are CCR7+$CD45RA^-$.

40. The ex vivo process of any of claims 37-39, wherein the composition is characterized by:

(a)

(i) at least 60% of the T cells in the composition are viable;

(ii) at least 25% of the T cells of the composition are CAR+ T cells;

(iii) at least 85% of the CD8+CAR+ T cells in the composition are CCR7+; and

(iv) at least 90% of the CD4+ CAR+ T cells in the composition are CCR7+;

(b)

(i) at least 60% of the T cells in the composition are viable,

(ii) at least 25% of the T cells of the composition are CAR+; and

(iii) greater than at or about 40% of the CAR+ T cells in the composition are CCR7+CD45RA+; or

(c)

(i) at least 60% of the T cells in the composition are viable;

(ii) at least 25% of the T cells of the composition are CAR+; and

(iii) greater than 20% of the CAR+ T cells in the composition are CCR7+CD45RA-.