CD40L-SPECIFIC TN3-DERIVED SCAFFOLDS AND METHODS OF USING THE SAME IN THE TREATMENT AND PREVENTION OF RHEUMATOID ARTHRITIS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority to U.S. Provisional Patent Application No. 63/337,274, filed May 2, 2022; U.S. Provisional Patent Application No. 63/322,379, filed March 22, 2022, and U.S. Provisional Patent Application No. 63/249,552, filed September 28, 2021, each of which is incorporated by reference herein in their entirety for all purposes.

REFERENCE TO AN ELECTRONIC SEQUENCE LISTING

[0002] The contents of the electronic sequence listing (HOPA_034_01WO_SeqList_ST26.xml; Size: 24,511 bytes; and Date of Creation: September 22, 2022) is herein incorporated by reference in its entirety.

TECHNICAL FIELD

[0003] The present disclosure is related to compositions comprising a Tn3 scaffold and methods using the same in the treatment prevention of rheumatoid arthritis.

BACKGROUND

[0004] Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that is associated with significant morbidity and mortality. The disease is characterized by inflammation of the synovial joints that can result in pain, swelling, and joint damage with secondary deformity and progressive disability. Worldwide, the prevalence of RA is estimated to be between 0.6-1.1% with variations across geographical regions. The incidence is 2-3 times higher in women than in men with a peak age of onset between 35-55 years of age. Uncontrolled active RA causes joint damage, disability, and decreased quality of life; comorbidities include cardiovascular disease and osteoporosis, and reduced life expectancy.

[0005] Despite the presence of existing therapeutic agents for the treatment of RA, there is a need for new treatments to reduce disease activity, because only a minority of subjects achieve clinical remission.

BRIEF SUMMARY

[0006] Provided are methods for treating rheumatoid arthritis in a subject in need thereof comprising administering a Tn3 scaffold comprising a CD40L-specific monomer subunit to the subject. In examples, the Tn3 scaffold specifically binds to CD40L. In examples, the monomer subunit comprises seven beta strands designated A, B, C, D, E, F, and G, and six loop regions designated AB, BC, CD, DE, EF, and FG, wherein the AB loop comprises SEQ ID NO: 11, the BC loop comprises SEQ ID NO: 12, the CD loop comprises SEQ ID NO: 13, the DE loop comprises SEQ ID NO: 14, the EF loop comprises SEQ

ID NO: 15, and the FG loop SEQ ID NO: 16, wherein the Tn3 scaffold comprising the CD40L-specific monomer subunit is administered at a dose of about 1500 mg, and wherein the Tn3 scaffold is administered once about every 2 weeks for at least 2 doses, and is administered about once a month thereafter.

[0006a] In one aspect, the present disclosure refers to a use of a Tn3 scaffold in the manufacture of a medicament for treating rheumatoid arthritis in a subject in need thereof, wherein the Tn3 scaffold comprises a CD40L-specific monomer subunit; wherein the monomer subunit comprises seven beta strands designated A, B, C, D, E, F, and G, and six loop regions designated AB, BC, CD, DE, EF, and FG, wherein the AB loop comprises SEQ ID NO: 11, the BC loop comprises SEQ ID NO: 12, the CD loop comprises SEQ ID NO: 13, the DE loop comprises SEQ ID NO: 14, the EF loop comprises SEQ ID NO: 15, and the FG loop SEQ ID NO: 16, wherein the Tn3 scaffold comprising the CD40L-specific monomer subunit is to be administered at a dose of about 1500 mg, and wherein the Tn3 scaffold is to be administered once about every 2 weeks for at least 2 doses, and is to be administered about once a month thereafter.

[0007] Provided are methods of treating rheumatoid arthritis in a subject in need thereof comprising: administering a Tn3 scaffold comprising a CD40L-specific monomer subunit to the subject; wherein the Tn3 scaffold specifically binds to CD40L; wherein the monomer subunit comprises seven beta strands designated A, B, C, D, E, F, and G, and six loop regions designated AB, BC, CD, DE, EF, and FG, wherein the AB loop comprises SEQ ID NO: 11, the BC loop comprises SEQ ID NO: 12, the CD loop comprises SEQ ID NO: 13, the DE loop comprises SEQ ID NO: 14, the EF loop comprises SEQ ID NO: 15, and the FG loop comprises SEQ ID NO: 16, wherein the Tn3 scaffold comprising the CD40L-specific monomer subunit is administered at a dose of about 1500 mg, and wherein the Tn3 scaffold is administered once about every 2 weeks for at least 3 doses, and is administered about once a month thereafter.

[0007a] In another aspect, the present disclosure refers to a use of a Tn3 scaffold in the manufacture of a medicament for treating rheumatoid arthritis in a subject in need thereof, wherein the Tn3 scaffold comprises a CD40L-specific monomer subunit; wherein the monomer subunit comprises seven beta strands designated A, B, C, D, E, F, and G, and six loop regions designated AB, BC, CD, DE, EF, and FG, wherein the AB loop comprises SEQ ID NO: 11, the BC loop comprises SEQ ID NO: 12, the CD loop comprises SEQ ID NO: 13, the DE loop comprises SEQ ID NO: 14, the EF loop comprises SEQ ID NO: 15, and the FG loop comprises SEQ ID NO: 16, wherein the Tn3 scaffold comprising the CD40L-specific monomer subunit is to be administered at a dose of about 1500 mg, and wherein the Tn3 scaffold is to be administered once about every 2 months for at least 2 doses.

[0008] Provided are methods of treating rheumatoid arthritis in a subject in need thereof comprising: administering a Tn3 scaffold comprising a CD40L-specific monomer subunit to the subject; wherein the Tn3 scaffold specifically binds to CD40L; wherein the monomer subunit comprises seven beta strands designated A, B, C, D, E, F, and G, and six loop regions designated AB, BC, CD, DE, EF, and FG, wherein the AB loop comprises SEQ ID NO: 11, the BC loop comprises SEQ ID NO: 12, the CD

loop comprises SEQ ID NO: 13, the DE loop comprises SEQ ID NO: 14, the EF loop comprises SEQ ID NO: 15, and the FG loop comprises SEQ ID NO: 16, wherein the Tn3 scaffold comprising the CD40L-specific monomer subunit is administered at a dose of about 1500 mg, and wherein the Tn3 scaffold is administered once about every 2 months for at least 2 doses.

[0009] Provided are methods for treating rheumatoid arthritis in a subject in need thereof comprising: administering a Tn3 scaffold comprising a CD40L-specific monomer subunit to the subject; wherein the Tn3 scaffold specifically binds to CD40L; wherein the monomer subunit comprises seven beta strands designated A, B, C, D, E, F, and G, and six loop regions designated AB, BC, CD, DE, EF, and FG, wherein the AB loop comprises SEQ ID NO: 11, the BC loop comprises SEQ ID NO: 12, the CD loop comprises SEQ ID NO: 13, the DE loop comprises SEQ ID NO: 14, the EF loop comprises SEQ ID NO: 15, and the FG loop comprises SEQ ID NO: 16, wherein the Tn3 scaffold comprising the CD40L-specific monomer subunit is administered at a dose of about 3000 mg, and wherein the Tn3 scaffold is administered about once, once a month, once about every two months, or once about every three months.

[0009a] In yet another aspect, the present disclosure refers to a use of a Tn3 scaffold in the manufacture of a medicament for treating rheumatoid arthritis in a subject in need thereof, wherein the Tn3 scaffold comprises a CD40L-specific monomer subunit; wherein the monomer subunit comprises seven beta strands designated A, B, C, D, E, F, and G, and six loop regions designated AB, BC, CD, DE, EF, and FG, wherein the AB loop comprises SEQ ID NO: 11, the BC loop comprises SEQ ID NO: 12, the CD loop comprises SEQ ID NO: 13, the DE loop comprises SEQ ID NO: 14, the EF loop comprises SEQ ID NO: 15, and the FG loop comprises SEQ ID NO: 16, wherein the Tn3 scaffold comprising the CD40L-specific monomer subunit is to be administered at a dose of about 3000 mg, and wherein the Tn3 scaffold is to be administered about once, once a month, once about every two months, or once about every three months.

[0010] In examples, the Tn3 scaffold is administered in combination with a second therapy. In examples, the second therapy comprises an anti-inflammatory agent, an anti-pain agent, a Disease-modifying Antirheumatic Drug (DMARD), a corticosteroid, or an immune system modifying agent. In examples, the DMARD is a conventional DMARD (cDMARD) or a biologic DMARD (bDMARD). In examples, the

DMARD is the cDMARD, and wherein the cDMARD is selected from the group consisting of: hydroxychloroquine, leflunomide, sulfasalazine, tofacitinib, and combinations thereof. In examples, the DMARD is the bDMARD, and wherein the bDMARD is selected from the group consisting of: etanercept, infliximab, adalimumab, certolizumab, and golimumab. In examples, the Tn3 scaffold is administered intravenously. In examples, the intravenous administration comprises an infusion. In examples, the Tn3 scaffold comprises two CD40L-specific monomer subunits connected in tandem. In examples, the Tn3 scaffold binds CD40L and prevents binding of CD40L to CD40 and/or disrupts CD40 mediated signaling. In examples, at least one CD40L-specific monomer subunit is fused or conjugated to a heterologous moiety selected from the group consisting of: a protein, a peptide, a protein domain, a linker, a drug, a toxin, a cytotoxic agent, an imaging agent, a radionuclide, a radioactive compound, an organic polymer, an inorganic polymer, a polyethylene glycol (PEG), biotin, an albumin, a human serum albumin (HSA), a HSA FcRn binding portion, an antibody, a domain of an antibody, an antibody fragment, a single chain antibody, a domain antibody, an albumin binding domain, an enzyme, a ligand, a receptor, a binding peptide, a non-FnIII scaffold, an epitope tag, a recombinant polypeptide polymer, and a cytokine. In examples, at least one CD40L-specific monomer subunit is conjugated to PEG or is fused to HSA. In examples, the HSA is a variant HSA comprising the amino acid sequence of SEQ ID NO: 4. In examples, the Tn3 scaffold comprises the sequence of SEQ ID NO: 1. In examples, a first dose of the Tn3 scaffold is administered at about 13 to about 25 mg/min, a second dose and third dose are administered at about 25 mg/min, and a fourth dose is administered at about 17 to about 33 mg/min. In examples, a first dose of the Tn3 scaffold is administered at about 8 to about 17 mg/min, and a second dose and third dose are administered at about 13 mg/min. In examples, a first dose of the Tn3 scaffold is about 1500 mg and subsequent doses are about 1500 mg or about 3000 mg. In examples, the first and a second dose of the Tn3 scaffold are about 1500 mg and the subsequent doses are about 3000 mg. In examples, a first dose is administered over 120 min or 180 min and subsequent doses are administered over 60 or 90 min. In examples, a Tn3 scaffold is administered once. In examples, a Tn3 scaffold is administered quarterly. In examples, a quarterly administration of the Tn3 scaffold is equally efficacious or more efficacious than more frequent administrations of the Tn3 scaffold as determined by change from baseline in DAS28-CRP in a treated subject. In examples, the change from baseline of the DAS28-CRP is determined quarterly. In examples, the change from baseline of the DAS28-CRP is determined monthly. In examples, the change from baseline of the DAS28-CRP is determined yearly. In examples, the quarterly administration of the Tn3 scaffold confers sustained treatment efficacy in the subject in need as compared to an otherwise comparable subject undergoing more frequent administrations of the Tn3 scaffold as determined by a treatment assessment, and wherein the sustained treatment efficacy is of at least or at most about 15 days, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 8 months, 10 months, 1 year, or 1.5 years. In examples, a treatment assessment is determined quarterly.

[0011] Provided herein are methods for treating RA in a subject in need thereof comprising administering a Tn3 scaffold comprising a CD40L-specific monomer subunit to the subject. In examples,

the Tn3 scaffold specifically binds to CD40L. In examples, the monomer subunit comprises seven beta strands designated A, B, C, D, E, F, and G, and six loop regions designated AB, BC, CD, DE, EF, and FG, wherein the AB loop comprises SEQ ID NO: 11, the BC loop comprises SEQ ID NO: 12, the CD loop comprises SEQ ID NO: 13, the DE loop comprises SEQ ID NO: 14, the EF loop comprises SEQ ID NO: 15, and the FG loop SEQ ID NO: 16. In examples, the Tn3 scaffold comprising the CD40L-specific monomer subunit is administered at a dose of about 1500 mg. In examples, the Tn3 scaffold is administered once about every 2 weeks for at least 2 doses, and is administered about once a month thereafter.

[0012] Provided herein are methods for treating rheumatoid arthritis in a subject in need thereof comprising administering a Tn3 scaffold comprising a CD40L-specific monomer subunit to the subject. In examples, the Tn3 scaffold specifically binds to CD40L. In examples, the monomer subunit comprises seven beta strands designated A, B, C, D, E, F, and G, and six loop regions designated AB, BC, CD, DE, EF, and FG, wherein the AB loop comprises SEQ ID NO: 11, the BC loop comprises SEQ ID NO: 12, the CD loop comprises SEQ ID NO: 13, the DE loop comprises SEQ ID NO: 14, the EF loop comprises SEQ ID NO: 15, and the FG loop comprises SEQ ID NO: 16. In examples, the Tn3 scaffold comprising the CD40L-specific monomer subunit is administered at a dose of about 1500 mg. In examples, the Tn3 scaffold is administered once about every 2 weeks for at least 3 doses, and is administered about once a month thereafter.

[0013] Provided herein are methods for treating rheumatoid arthritis in a subject in need thereof comprising administering a Tn3 scaffold comprising a CD40L-specific monomer subunit to the subject. In examples, the Tn3 scaffold specifically binds to CD40L. In examples, the monomer subunit comprises seven beta strands designated A, B, C, D, E, F, and G, and six loop regions designated AB, BC, CD, DE, EF, and FG, wherein the AB loop comprises SEQ ID NO: 11, the BC loop comprises SEQ ID NO: 12, the CD loop comprises SEQ ID NO: 13, the DE loop comprises SEQ ID NO: 14, the EF loop comprises SEQ ID NO: 15, and the FG loop comprises SEQ ID NO: 16. In examples, the Tn3 scaffold comprising the CD40L-specific monomer subunit is administered at a dose of about 1500 mg. In examples, the Tn3 scaffold is administered once about every 2 months for at least 2 doses.

[0014] Provided herein are methods for treating rheumatoid arthritis in a subject in need thereof comprising administering a Tn3 scaffold comprising a CD40L-specific monomer subunit to the subject. In examples, the Tn3 scaffold specifically binds to CD40L. In examples, the monomer subunit comprises seven beta strands designated A, B, C, D, E, F, and G, and six loop regions designated AB, BC, CD, DE, EF, and FG, wherein the AB loop comprises SEQ ID NO: 11, the BC loop comprises SEQ ID NO: 12, the CD loop comprises SEQ ID NO: 13, the DE loop comprises SEQ ID NO: 14, the EF loop comprises SEQ ID NO: 15, and the FG loop comprises SEQ ID NO: 16. In examples, the Tn3 scaffold comprising the CD40L-specific monomer subunit is administered at a dose of about 3000 mg. In examples, the Tn3 scaffold is administered about once a month, once about every two months, or once about every three months.

[0015] These and other examples are described below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] The accompanying figures, which are incorporated herein and form a part of the specification, illustrate some, but not the only or exclusive, example aspects and/or features. It is intended that the aspects and figures disclosed herein are to be considered illustrative rather than limiting.

[0017] **FIG. 1** shows an exemplary study flow diagram. The Tn3 scaffold is VIB4920. VIB4920 comprises a bivalent CD40L-specific Tn3 protein fused to a human serum albumin (HSA) and has the sequence shown in SEQ ID NO:1. Approximately 75 subjects randomized (1:1:1:1:1), placebo-controlled, parallel design. All subjects are dosed 4 times total, with each dose administered on days 1, 15, 29 and 57, and doses that are not VIB4920 are placebo. Study population comprises adults (≥ 18 years of age) with active, moderate-to-severe adult-onset RA (e.g., DAS28-CRP > 3.2; ≥ 4 tender and ≥ 4 swollen joints) and presence of serum rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPAs) with inadequate response to Methotrexate (MTX), cDMARD, or anti-TNFα agent and no prior treatment with rituximab or B cell depletive agents.

[0018] **FIG. 2** shows the change from baseline in DAS28-CRP in placebo, VIB4920 3000mg x 1, VIB4920 1500mg x 2, VIB4920 3000mg x 2, and VIB4920 1500mg x 4 groups.

[0019] **FIG. 3** shows the change from baseline in CDAI in placebo, VIB4920 3000mg x 1, VIB4920 1500mg x 2, VIB4920 3000mg x 2, and VIB4920 1500mg x 4 groups. Summary statistics for day 113 are listed.

[0020] **FIG. 4** shows the change from baseline in SDAI in placebo, VIB4920 3000mg x 1, VIB4920 1500mg x 2, VIB4920 3000mg x 2, and VIB4920 1500mg x 4 groups. Summary statistics for day 113 are listed.

[0021] **FIG. 5** shows the change from baseline in Swollen Joint Count in placebo, VIB4920 3000mg x 1, VIB4920 1500mg x 2, VIB4920 3000mg x 2, and VIB4920 1500mg x 4 groups. Summary statistics for day 113 are listed.

[0022] **FIG. 6** shows the change from baseline in Tender Joint Count in placebo, VIB4920 3000mg x 1, VIB4920 1500mg x 2, VIB4920 3000mg x 2, and VIB4920 1500mg x 4 groups. Summary statistics for day 113 are listed.

[0023] **FIG. 7** shows the change from baseline in Physician Global Assessment in placebo, VIB4920 3000mg x 1, VIB4920 1500mg x 2, VIB4920 3000mg x 2, and VIB4920 1500mg x 4 groups. Summary statistics for day 113 are listed.

[0024] **FIG. 8** shows the change from baseline in Patient Global Assessment in placebo, VIB4920 3000mg x 1, VIB4920 1500mg x 2, VIB4920 3000mg x 2, and VIB4920 1500mg x 4 groups.

[0025] **FIG. 9** shows the change from baseline in CRP in placebo, VIB4920 3000mg x 1, VIB4920 1500mg x 2, VIB4920 3000mg x 2, and VIB4920 1500mg x 4 groups.

CLAIMS

We claim:

1. Use of a Tn3 scaffold in the manufacture of a medicament for treating rheumatoid arthritis in a subject in need thereof,

wherein the Tn3 scaffold comprises a CD40L-specific monomer subunit;

wherein the monomer subunit comprises seven beta strands designated A, B, C, D, E, F, and G, and six loop regions designated AB, BC, CD, DE, EF, and FG, wherein the AB loop comprises SEQ ID NO: 11, the BC loop comprises SEQ ID NO: 12, the CD loop comprises SEQ ID NO: 13, the DE loop comprises SEQ ID NO: 14, the EF loop comprises SEQ ID NO: 15, and the FG loop SEQ ID NO: 16,

wherein the Tn3 scaffold comprising the CD40L-specific monomer subunit is to be administered at a dose of about 1500 mg, and

wherein the Tn3 scaffold is to be administered once about every 2 weeks for at least 2 doses, and is to be administered about once a month thereafter.

2. Use of a Tn3 scaffold in the manufacture of a medicament for treating rheumatoid arthritis in a subject in need thereof,

wherein the Tn3 scaffold comprises a CD40L-specific monomer subunit;

wherein the monomer subunit comprises seven beta strands designated A, B, C, D, E, F, and G, and six loop regions designated AB, BC, CD, DE, EF, and FG, wherein the AB loop comprises SEQ ID NO: 11, the BC loop comprises SEQ ID NO: 12, the CD loop comprises SEQ ID NO: 13, the DE loop comprises SEQ ID NO: 14, the EF loop comprises SEQ ID NO: 15, and the FG loop comprises SEQ ID NO: 16,

wherein the Tn3 scaffold comprising the CD40L-specific monomer subunit is to be administered at a dose of about 1500 mg, and

wherein the Tn3 scaffold is to be administered once about every 2 months for at least 2 doses.

3. Use of a Tn3 scaffold in the manufacture of a medicament for treating rheumatoid arthritis in a subject in need thereof,

wherein the Tn3 scaffold comprises a CD40L-specific monomer subunit;

wherein the monomer subunit comprises seven beta strands designated A, B, C, D, E, F, and G, and six loop regions designated AB, BC, CD, DE, EF, and FG, wherein the AB loop comprises SEQ ID NO: 11, the BC loop comprises SEQ ID NO: 12, the CD loop comprises SEQ ID NO: 13, the DE loop comprises SEQ ID NO: 14, the EF loop comprises SEQ ID NO: 15, and the FG loop comprises SEQ ID NO: 16,

wherein the Tn3 scaffold comprising the CD40L-specific monomer subunit is to be administered at a dose of about 3000 mg, and

wherein the Tn3 scaffold is to be administered about once, once a month, once about every two months, or once about every three months.

4. The use of any one of claims 1-3, wherein the Tn3 scaffold is to be administered in combination with a second therapy.

5. The use of claim 4, wherein the second therapy comprises an anti-inflammatory agent, an anti-pain agent, a Disease-modifying Antirheumatic Drug (DMARD), a corticosteroid, or an immune system modifying agent.

6. The use of any one of claims 1-5, wherein the Tn3 scaffold is to be administered intravenously.

7. The use of any one of claims 1-6, wherein the Tn3 scaffold comprises two CD40L-specific monomer subunits connected in tandem.

8 The use of any one of claims 1-7, wherein the Tn3 scaffold binds CD40L and prevents binding of CD40L to CD40 and/or disrupts CD40 mediated signaling.

9. The use of any one of claims 1-8, wherein at least one CD40L-specific monomer subunit is fused to a human serum albumin (HSA).

10. The use of claim 9, wherein the HSA is a variant HSA comprising the amino acid sequence of SEQ ID NO: 4.

11. The use of any one of claims 1-10, wherein the Tn3 scaffold comprises the sequence of SEQ ID NO: 1.

12. The use of any one of claims 1-11, wherein the Tn3 scaffold is Dazodalibep.

13. The use of any one of claims 1-12, wherein a first dose of the Tn3 scaffold is about 1500 mg and subsequent doses are about 1500 mg or about 3000 mg.

14. The use of claim 13, wherein the first and a second dose of the Tn3 scaffold are about 1500 mg and the subsequent doses are about 3000 mg.

15. The use of any one of claims 1-14, wherein the Tn3 scaffold is to be administered quarterly.

16. The use of claim 15, wherein the quarterly administration of the Tn3 scaffold confers sustained treatment efficacy in the subject in need as compared to an otherwise comparable subject undergoing more frequent administrations of the Tn3 scaffold as determined by a treatment assessment, and wherein the sustained treatment efficacy is of at least or at most about 15 days, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 8 months, 10 months, 1 year, or 1.5 years.

17. The use of claim 16, wherein the treatment assessment is to be determined quarterly.

18. The use of any one of claims 1-17, wherein the CD40L-specific monomer subunit comprises the seven beta strands designated A, B, C, D, E, F, and G, wherein the beta strand A comprises SEQ ID NO: 5, the beta strand B comprises SEQ ID NO: 6, the beta strand C comprises SEQ ID NO: 17, the beta strand D comprises SEQ ID NO: 18, the beta strand E comprises SEQ ID NO: 19, the beta strand F comprises SEQ ID NO: 20, the beta strand G comprises SEQ ID NO: 21.

19. The use of any one of claims 1-18, wherein the CD40L-specific monomer subunit comprises the polypeptide of SEQ ID NO: 22, and wherein the second CD40L-specific monomer subunit comprises the polypeptide of SEQ ID NO: 25.

20. The use any one of claims 1-19, wherein the CD40L-specific monomer subunit comprises the polypeptide of SEQ ID NO: 22

21. The use of any one of claims 1-20, wherein the CD40L-specific monomer subunit comprises the polypeptide of SEQ ID NO: 25.