by an European League Against Rheumatism (EULAR) Sjögren's Syndrome Patient Reported Index (ESSPRI) score of ≥ 5, considered as the cut-off point for "unsatisfactory symptom state" but with lower systemic disease activity (with EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) score < 5] represents a large subset of SS patients who have been excluded from recent trials despite the substantial disease burden and overall unacceptable health status.

[0006] About 15-20% of SS patients present with systemic manifestations beyond the commonly affected exocrine glands (salivary and ocular). Moderate to high systemic activity in SS patients can be defined by ESSDAI ≥ 5. These manifestations most commonly include arthritis, lung disease, renal disease, vasculitis, neuropathies, and autonomic nervous system dysfunction, which accompany glandular involvement. Moderate to high disease activity is not only debilitating but can also lead to dysfunction of the affected organ(s), or to hematologic pathologies, including thrombocytopenia and lymphoma, that have been associated with increased risk of mortality. No biologics or disease-modifying anti-rheumatic drugs (DMARDs) have been shown to be efficacious in significantly reducing SS systemic disease activity. Currently, there are no approved immunomodulating agents or evidence-based therapeutic guidelines available for treatment of the extra glandular manifestations of SS. Therefore, standard of care for extra glandular manifestations varies widely and is based on local practices, expert opinion, and personal experience of the treating physicians.

[0007] There is a need for new treatments aimed at to reduce the substantial disease burden and overall unacceptable health status.

BRIEF SUMMARY

[0008] Provided herein are methods for treating Sjögren's syndrome (SS) 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, about 2500 mg, or about 3000 mg.

[0008a] In one aspect, the present disclosure refers to a use of a Tn3 scaffold in the manufacture of a medicament for treating Sjögren's syndrome (SS) in a subject in need thereof, wherein the

Tn3 scaffold comprises two CD40L-specific monomer subunits; wherein the Tn3 scaffold is to be administered with a human serum albumin to the subject; wherein the monomer subunits comprise 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, and wherein the Tn3 scaffold is to be administered at a dose of about 1500 mg every 4 weeks.

[0009] Provided herein are methods of treating Sjögren's syndrome (SS) in a subject in need thereof comprising administering a Tn3 scaffold at a dose of about 1500 mg, about 2500 mg, or about 3000 mg to the subject, wherein the Tn3 scaffold comprises SEQ ID NO: 1.

[0010] Provided are methods for treating Sjögren's syndrome (SS) 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 SEQ ID NO: 16, wherein the Tn3 scaffold comprising the CD40L-specific monomer subunit is administered at a dose of about 1500 mg, about 2500 mg, or about 3000 mg. In examples, at least one 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. In examples, a subject has a European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) score ≥ 5. In examples, an ESSDAI score is assessed based on the ESSDAI domains consisting of cutaneous, renal, articular, muscular, hematological, glandular, constitutional, lymphadenopathic, and biological. In examples, a subject has (a) said ESSDAI score < 5, (b) EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) score ≥ 5, and (c) whole stimulated salivary flow > 0.1 mL/min.

[0011] In examples, a Tn3 scaffold is administered as an induction dose and as a maintenance dose thereafter. In examples, an induction dose comprises administering a Tn3 scaffold once about every 2 weeks for at least 3 doses. In examples, a maintenance dose comprises administering a Tn3 scaffold once about every 4 weeks for at least 4 doses. In examples, the time between an induction dose and a maintenance dose is about 4 weeks. In examples, a Tn3 scaffold is administered once about every 4 weeks, once about every 2 months, once about every 3 months, once about every 4 months, or once about every 6 months. In examples, a Tn3 scaffold is administered for at least 4 doses. In examples, a Tn3 scaffold is administered for at least 5 doses. In examples, a Tn3 scaffold is administered intravenously, subcutaneously, orally, intramuscularly, intrathecally, sublingually, rectally, vaginally, cutaneously, systemically, topically, transdermally, or by way of inhalation. In examples, a Tn3 scaffold is administered intravenously. In examples, a Tn3 scaffold comprises two CD40L-specific monomer subunits connected in tandem. In examples, the two CD40L-specific monomer subunits each comprise SEQ ID NO: 3. In examples, the CD40L-specific monomer subunits are connected by a linker.

In examples, at least one CD40L-specific monomer subunit is fused or conjugated to a polyethylene glycol (PEG) directly. In examples, at least one CD40L-specific monomer subunit is fused or conjugated to a polyethylene glycol (PEG) via a linker. In examples, the linker comprises a peptide linker. In examples, the linker comprises SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, or SEQ ID NO: 10. In examples, at least one CD40L-specific monomer subunit is fused or conjugated to an albumin. In examples, the albumin is human serum albumin (HSA). In examples, the HSA is a variant HSA comprising SEQ ID NO: 4.

[0012] Provided are methods of treating Sjögren's syndrome (SS) in a subject in need thereof. In examples, a method may comprise administering a Tn3 scaffold at a dose of about 1500 mg, about 2500 mg, or about 3000 mg to the subject of need. In examples, a method may comprise administering a Tn3 scaffold comprised of SEQ ID NO: 1. In examples, a Tn3 scaffold is administered as an induction dose and as one or more maintenance doses thereafter. In examples, an induction dose and maintenance doses are the same amount. In examples, an induction dose and maintenance doses are different amounts. In examples, least one dose is 3000 mg. In examples, an induction dose and at least one maintenance dose are administered about 1 month apart, about 2 months apart, about 3 months apart, about 4 months, or about 6 months apart. In examples, an induction dose comprises administering a Tn3 scaffold about every 2 weeks for at least 3 doses and the maintenance dose comprises administering a Tn3 scaffold once about every 4 weeks for at least 4 doses. In examples, a Tn3 scaffold comprises SEQ ID NO: 1. In examples, the method is effective in reducing a ESSDAI score as compared to an otherwise comparable method wherein the subject receives an equivalent administration. In examples, the reduction is of at least about 1 point, 2 points, 3 points, 4 points, or 5 points. In examples, the reduction is of at least about 6 points.

[0012a] In another aspect, the present disclosure refers to a use of a Tn3 scaffold comprising SEQ ID NO: 1 in the manufacture of a medicament for treating Sjögren's syndrome (SS) in a subject in need thereof, wherein the Tn3 scaffold is to be administered at a dose of about 1500 mg every 4 weeks.

[0012b] In yet another aspect, the present disclosure refers to a use of a Tn3 scaffold in the manufacture of a medicament for treating Sjögren's syndrome (SS) in a subject in need thereof, wherein the Tn3 comprises two CD40L-specific monomer subunits and a human serum albumin; wherein the monomer subunits comprise 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, and wherein the Tn3 scaffold is to be administered at a dose of about 3000 mg every 12 weeks.

[0012c] In another aspect, the present disclosure refers to a use of Tn3 scaffold comprising SEQ ID NO: 1 in the manufacture of a medicament for treating Sjögren's syndrome (SS) in a subject in need thereof, wherein the Tn3 scaffold is to be administered at a dose of about 3000 mg every 12 weeks.

[0012d] In another aspect, the present disclosure refers to a use of a Tn3 scaffold comprising SEQ ID NO: 1 in the manufacture of a medicament for treating Sjögren's syndrome (SS) in a subject in need thereof, wherein the Tn3 scaffold is to be administered at a dose of about 3000 mg every 12 weeks, and wherein the subject is to receive a loading dose of 3000 mg of the Tn3 scaffold about four weeks after the first dose.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] FIG. 1 shows an exemplary study flow diagram comprising adults with moderate to severe (moderate to high) systemic disease activity defined by ESSDAI ≥ 5, and presence of anti-Ro autoantibodies and/or rheumatoid factor (RF). Seventy four subjects were randomized (1:1) to receive VIB4920 1500 mg or placebo intravenously once every 2 weeks x 3 doses, then once every 4 weeks (Q4W) for 4 additional doses (Stage I). Starting on day 169, subjects randomized to VIB4920 received placebo Q4W for 5 doses and subjects randomized to placebo received VIB4920 Q4W for 5 doses (Stage II). Randomization was stratified by EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) score at screening (< 10 points vs ≥ 10 points). Δ = delta; D = days; EoS = End of Study; EP = endpoint; ESSDAI = European League

CLAIMS

1. Use of a Tn3 scaffold in the manufacture of a medicament for treating Sjögren's syndrome (SS) in a subject in need thereof, wherein the

Tn3 scaffold comprises two CD40L-specific monomer subunits; wherein the Tn3 scaffold is to be administered with a human serum albumin to the subject;

wherein the monomer subunits comprise 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,
and wherein the Tn3 scaffold is to be administered at a dose of about 1500 mg every 4 weeks.

2. The use of claim 1, wherein the subject has a European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) score ≥ 5.

3. The use of claim 1, wherein the subject has:
(a) a ESSDAI score < 5, and
(b) a EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) score ≥ 5.

4. The use of claim 3, wherein the subject has:
whole stimulated salivary flow > 0.1 mL/min.

5. The use of claim 1, wherein the subject is to receive a loading dose of 1500 mg about every 2 weeks for at least 3 doses.

6. The use of claim 1, wherein the subject is to receive a loading dose of 1500 mg of the Tn3 scaffold about two weeks after the first dose.

7. The use of claim 1, wherein beta strand A comprises SEQ ID NO: 5, beta strand B comprises SEQ ID NO: 6, beta strand C comprises SEQ ID NO: 17, beta strand D

comprises SEQ ID NO: 18, beta strand E comprises SEQ ID NO: 19, beta strand F comprises SEQ ID NO: 20, and beta strand G comprises SEQ ID NO: 21.

8. The use of claim 1, wherein the Tn3 scaffold comprises two CD40L-specific monomer subunits connected in tandem.

9. The use of claim 8, wherein the two CD40L-specific monomer subunits each comprise SEQ ID NO: 3.

10. The use of claim 8, wherein the two CD40L-specific monomer subunits are connected by a linker.

11. The use of claim 8, wherein at least one CD40L-specific monomer subunit is fused or conjugated to a polyethylene glycol (PEG) via a linker selected from the group consisting of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9 and SEQ ID NO: 10.

12. The use of claim 8, wherein at least one CD40L-specific monomer subunit is fused or conjugated to an albumin.

13. The use of claim 8, wherein the albumin is a human serum albumin (HSA).

14. The use of claim 13, wherein the HSA is a variant HSA comprising SEQ ID NO: 4.

15. The use of claim 1, wherein the Tn3 scaffold comprises SEQ ID NO: 1.

16. Use of a Tn3 scaffold comprising SEQ ID NO: 1 in the manufacture of a medicament for treating Sjögren's syndrome (SS) in a subject in need thereof, wherein the Tn3 scaffold is to be administered at a dose of about 1500 mg every 4 weeks.

17. The use of claim 16, wherein prior to the dose of about 1500 mg every 4 weeks, the subject is to receive a loading dose of once about every 2 weeks for at least 3 doses.

18. The use of claim 16, wherein the subject is to receive a loading dose of 1500 mg of the Tn3 scaffold about two weeks after the first dose.

19. Use of a Tn3 scaffold comprising SEQ ID NO: 1 in the manufacture of a medicament for treating Sjögren's syndrome (SS) in a subject in need thereof, wherein the Tn3 scaffold is to be administered at a dose of about 1500 mg every 4 weeks, and wherein a loading dose of 1500 mg of the Tn3 scaffold is to be administered two weeks after the first dose.

20. Use of a Tn3 scaffold in the manufacture of a medicament for treating Sjögren's syndrome (SS) in a subject in need thereof, wherein the Tn3 comprises two CD40L-specific monomer subunits and a human serum albumin;

wherein the monomer subunits comprise 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,

and wherein the Tn3 scaffold is to be administered at a dose of about 3000 mg every 12 weeks.

21. The use of claim 20, wherein the subject has a European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) score ≥ 5.

22. The use of claim 20, wherein the subject has:

(a) a ESSDAI score < 5, and

(b) a EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) score ≥ 5.

23. The use of claim 22, wherein the subject has:

whole stimulated salivary flow > 0.1 mL/min.

24. The use of claim 20, wherein prior to the dose of about 3000 mg every 12 weeks, the subject is to be administered an initial dose of 3000 mg of the Tn3 scaffold followed by a second dose of 3000 mg four weeks later and a third dose of 3000 mg about 8 weeks after the second dose.

25. The use of claim 20, wherein the subject is to receive a loading dose of 3000 mg of the Tn3 scaffold about four weeks after the first dose.

26. The use of claim 20, wherein beta strand A comprises SEQ ID NO: 5, beta strand B comprises SEQ ID NO: 6, beta strand C comprises SEQ ID NO: 17, beta strand D comprises SEQ ID NO: 18, beta strand E comprises SEQ ID NO: 19, beta strand F comprises SEQ ID NO: 20, and beta strand G comprises SEQ ID NO: 21.

27. The use of claim 20, wherein the Tn3 scaffold comprises two CD40L-specific monomer subunits connected in tandem.

28. The use of claim 27, wherein the two CD40L-specific monomer subunits each comprise SEQ ID NO: 3.

29. The use of claim 27, wherein the two CD40L-specific monomer subunits are connected by a linker.

30. The use of claim 27, wherein at least one CD40L-specific monomer subunit is fused or conjugated to a polyethylene glycol (PEG) via a linker selected from the group consisting of: SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, or SEQ ID NO: 10.

31. The use of claim 27, wherein at least one CD40L-specific monomer subunit is fused or conjugated to an albumin.

32. The use of claim 31, wherein the albumin is a human serum albumin (HSA).

33. The use of claim 32, wherein the HSA is a variant HSA comprising SEQ ID NO: 4.

34. The use of claim 20, wherein the Tn3 scaffold comprises SEQ ID NO: 1.

35. Use of Tn3 scaffold comprising SEQ ID NO: 1 in the manufacture of a medicament for treating Sjögren's syndrome (SS) in a subject in need thereof, wherein the Tn3 scaffold is to be administered at a dose of about 3000 mg every 12 weeks.

36. The use of claim 35, wherein prior to the dose of about 3000 mg every 12 weeks, the subject is to be administered an initial dose of the Tn3 scaffold followed by a second dose four weeks later and a third dose about 8 weeks after the second dose.

37. The use of claim 35, wherein the subject is to receive a loading dose of 3000 mg of the Tn3 scaffold about four weeks after the first dose.

38. Use of a Tn3 scaffold comprising SEQ ID NO: 1 in the manufacture of a medicament for treating Sjögren's syndrome (SS) in a subject in need thereof, wherein the Tn3 scaffold is to be administered at a dose of about 3000 mg every 12 weeks, and wherein the subject is to receive a loading dose of 3000 mg of the Tn3 scaffold about four weeks after the first dose.