cells and long-lived plasma cells (T. M. Foy *et al.*, 1994; T. M. Foy *et al.*, 1993; S. Han *et al.*, 1995; T. Kawabe *et al.*, 1994). CD40 or CD40L defects in humans lead to X-linked hyperimmunoglobulin syndrome, a disease characterized by impaired isotype class switching, which manifests as high levels of serum IgM with low to no detectable IgG, IgA or IgE and increased susceptibility to infections (R. C. Allen *et al., 1993;* A. Aruffo *et al., 1993;* J. P. DiSanto *et al*., 1993).

[006] Fusion of a bivalent CD40L-specific Tn3 protein to human serum albumin (HSA) resulted in a molecule, *i.e.*, VIB4920, that was able to bind human CD40L and prevent its interaction with CD40 receptor. Consistent with this disruption in CD40L/CD40 interaction, VIB4920 was able to potently inhibit activation and differentiation of human B cells *in vitro* by blocking CD40 signaling events.

[007] Currently available methods are directed towards treating autoimmune diseases and not towards preventing such diseases. Further, conventional treatment options for autoimmune diseases include immunosuppressant drugs that are associated with a wide range of side effects. Thus, there is a need for better therapeutic alternatives for treating and preventing autoimmune diseases, in particular lupus nephritis. The present disclosure addresses these needs.

SUMMARY

[008] The description provides for a method for treating lupus nephritis in a subject in need thereof comprising: administering a Tn3 scaffold comprising a CD40L-specific monomer subunit to the subject; wherein the Tn3 scaffold 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 2 doses, and is administered about once a month thereafter.

[008a] In one aspect, the present disclosure refers to use of a Tn3 scaffold in the manufacture of a medicament for treating lupus nephritis in a subject in need thereof, wherein the Tn3 scaffold comprises a CD40L-specific monomer subunit, wherein the CD40L-specific 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 weeks for at least 2 doses and is to be administered about once a month thereafter.

[008b] In one aspect, the present disclosure refers to use of a Tn3 scaffold in the manufacture of a medicament for treating lupus nephritis in a subject in need thereof, wherein the Tn3 scaffold comprises a CD40L-specific monomer subunit, wherein the CD40L-specific 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, 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, and wherein the subject has Systemic Lupus Erythematosus.

[009] The description provides for a method for treating lupus nephritis in a subject in need thereof comprising: administering a Tn3 scaffold comprising a CD40L-specific monomer

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 is administered at a dose of about 1500 mg. In examples, cyclophosphamide is administered for at least about eight, ten, twelve or more weeks prior to the first administration of the Tn3 scaffold. In examples, the cyclophosphamide is administered for at least about eight weeks prior to the first administration of the Tn3 scaffold. In examples, the cyclophosphamide is administered for at least about ten weeks prior to the first administration of the Tn3 scaffold. In examples, the cyclophosphamide is administered for at least about twelve weeks prior to the first administration of the Tn3 scaffold.

[0013] In examples, the Tn3 scaffold is administered once about every two, three, four weeks, or about once a month. 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. 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.

[0014] In examples, the Tn3 scaffold is administered intravenously.

[0015] 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, the Tn3 scaffold (a) binds CD40L thereby reducing or preventing binding of CD40L to CD40; (b) reduces or eliminates CD40 mediated signaling; or (c) a and b. In examples, the 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 a human serum albumin (HSA). In examples, said HSA is a variant HSA having the amino acid sequence of SEQ ID NO: 4. In

examples, the Tn3 scaffold comprises the sequence of SEQ ID NO: 1. In examples, the Tn3 scaffold is VIB4920.

[0016] In examples, the subject is further administered prednisone. In examples, the subject received one or more standard of care therapies prior to the administration of the Tn3 scaffold. In examples, the standard of care therapy is MMF. In examples, the standard of care therapy is methylprednisolone. In examples, the standard of care therapy is cyclophosphamide. In examples, the standard of care therapy is prednisone.

[0017] Provided are methods of treating lupus nephritis comprising administering to a subject in need thereof: a) a preparative regime that comprises administration of at least one immunosuppressant in an amount sufficient to reduce an immune response in the subject; and b) about 1000-2000 mg of Dazodalibep, wherein the Dazodalibep is administered once about every 2 weeks for at least 2 doses, and is administered about once a month thereafter.

[0018] Provided are methods of treating lupus nephritis comprising administering to a subject in need thereof: a) a preparative regime that comprises: i. administration of an immunosuppressant in an amount sufficient to reduce an immune response in the subject; and ii. administration of a corticosteroid in an amount sufficient to reduce inflammation in the student; and b) about 1000-2000 mg of Dazodalibep, wherein the Dazodalibep is administered once about every 2 weeks for at least 2 doses, and is administered about once a month thereafter.

[0019] In examples, an immunosuppressant is selected from the group consisting of: Azathioprine, Mycophenolate mofetil, Cyclosporine, Methotrexate, Leflunomide, Cyclophosphamide, Chlorambucil, Nitrogen mustard, and combinations thereof. In examples, an immunosuppressant is selected from the group consisting of: azathioprine, mycophenolate mofetil, cyclophosphamide, and cyclosporine. In examples, an immunosuppressant is mycophenolate mofetil. In examples, an immunosuppressant is cyclophosphamide. In examples, an immunosuppressant is administered for at least about eight, nine, ten, eleven, twelve or more weeks prior to a first administration of the Dazodalibep. In examples, cyclophosphamide is administered every 4 weeks. In examples, cyclophosphamide is administered every 2 weeks. In examples, about 1200-1800 mg of the Dazodalibep is administered. In examples, about 1500 mg of Dazodalibep is administered. In examples, a preparative regimen further comprises

administering a corticosteroid to the subject. In examples, a corticosteroid is prednisone. In examples, administering of the corticosteroid is tapered.

[0020] In examples, in any of the preceding methods, a Tn3 scaffold monomer comprises a beta A strand that comprises SEQ ID NO: 5, SEQ ID NO: 23, or SEQ ID NO: 24, a beta B strand that comprises SEQ ID NO: 6, a beta C strand that comprises SEQ ID NO: 17, a beta D strand that comprises SEQ ID NO: 18, a beta E strand that comprises SEQ ID NO: 19, a beta F strand that comprises SEQ ID NO: 20, and a beta G strand that comprises SEQ ID NO: 21. In examples, the beta A strand consists of SEQ ID NO: 5. In examples, the beta A strand consists of SEQ ID NO: 23. In examples, the beta A strand consists of SEQ ID NO: 24. In examples, the beta B strand consists of SEQ ID NO: 6. In examples, the beta C strand consists of SEQ ID NO: 17. In examples, the beta D strand consists of SEQ ID NO: 18. In examples, the beta E strand consists of SEQ ID NO: 19. In examples, the beta F strand consists of SEQ ID NO: 20. In examples, the beta G strand consists of SEQ ID NO: 21.

DETAILED DESCRIPTION

[0021] Provided herein are Tn3 scaffolds that are anti-cluster of differentiation (CD) 40 ligand (CD40L)-third fibronectin type III (Fn3) protein domain of human Tenascin C (Tn3) protein fusion proteins and methods of using the same in autoimmune disease. In aspects, compositions and methods provided are utilized for the treatment of lupus nephritis.

[0022] Also provided are methods comprising administering Tn3 scaffolds with immunosuppressants and/or corticosteroids for the treatment of lupus nephritis.

Definitions:

[0023] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the subject matter pertains. All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entirety. In cases of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples described herein are illustrative only and are not intended to be limiting.

[0024] As used in this specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise.