THERAPIES FOR AUTOIMMUNE DISORDERS

RELATED APPLICATIONS

[0001] The present patent application claims the priority benefit of U.S. Provisional Patent Applications Ser. No. 63/627,788, filed January 31, 2024; 63/575,689, filed April 6, 2024; 63/708,634, filed October 17, 2024; 63/750,959, filed January 29, 2025. The content of each is hereby incorporated by reference in its entirety into this disclosure.

INCORPORATION BY REFERENCE OF AN ELECTRONIC SEQUENCE LISTING

[0002] This application contains a Sequence listing that has been submitted electronically in a computer readable format and is hereby incorporated by reference in its entirety. The computer readable file, 67806_Sequence.xlm, created January 29, 2025, is 51,752 bytes in size.

BACKGROUND

[0003] In autoimmune conditions, B cells contribute to disease pathology through several mechanisms, including the production of autoantibodies that target self-antigens, the activation of T cells via antigen presentation, and the secretion of pro-inflammatory cytokines that amplify immune responses. Autoantibodies can directly damage tissues, activate complement pathways, and perpetuate chronic inflammation, as seen in diseases like systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's disease (SiD), and multiple sclerosis (MS). Targeting B cells has become a cornerstone of therapy for many autoimmune diseases, with treatments such as monoclonal antibodies (e.g., rituximab and ocrelizumab) effectively depleting or modulating B cells to reduce disease activity and prevent long-term damage.

[0004] SLE is an autoimmune disease characterized by the production of autoantibodies against nuclear antigens, including doubled-stranded DNA (dsDNA) and other nuclear antigens (ANA), which trigger immune complex-induced inflammation in an array of different organs, such as the kidneys, the heart, the lungs, and the skin. Recently approved agents such as

belimumab, anifrolumab, and voclosporin have demonstrated clinical benefit in controlled clinical studies when added to standard therapies. However, none of these agents have demonstrated the routine ability to induce drug-free remissions. Further, despite these recent advances, increased mortality remains a significant concern in patient management.

[0005] While the immune defect in SLE is multifaceted, the central role of B cell abnormalities in the pathogenesis of SLE has recently been characterized. Aberrant immune tolerance mechanisms lead to dysregulation of B cell transcription factors, cytokines, and B cell-T cell interactions, resulting in altered B cell maturation, emergence of autoreactive B cells, and autoantibody production. Novel therapeutic approaches targeting the B-cell repertoire have been an active area of investigation in SLE, and in 2011, belimumab, a fully humanized monoclonal antibody targeting B cell-activity BAFF, became the first medication in 50 years approved by the US Food and Drug Administration to treat adult SLE. Disappointingly, monoclonal antibodies targeting the CD20 cell surface antigen demonstrated promising results in phase 2 studies that failed to be replicated in randomized controlled trials.

[0006] Recent data for CD19 CAR T treatment in severe SLE provides proof-of-concept that therapies inducing deeper depletion of tissue-resident B cell populations can achieve durable, treatment-free remissions in refractory SLE patients. A subsequent publication described a series of 5 patients with severe SLE refractory to multiple immunosuppressive drug treatments that achieved drug-free remission durable at a median follow-up of 8 months after a single infusion of CD19 CAR T cells. These data were recently updated with longer follow-up.

[0007] While these CAR-T cell therapies show encouraging potential efficacy, they are hampered by significant safety and/or tolerability issues that make use of a CAR-T-based approach impractical and ineffective for use in autoimmune disorders. In the context of CAR-T cell therapy relapsed/refractory B cell malignancies, there are numerous factors to be considered during the treatment, including the need for a bridging therapy or conditioning regimen prior to the infusion of CAR-T cell product. The infusion of CAR-T cells must be performed in a timely manner to control disease progression. The period between apheresis and CAR-T cell infusion can be weeks to months, and this time interval may lead to a treatment gap where some patients may experience disease progression and/or death. Therefore, for efficacy in B-cell malignancies, CAR-T therapy often requires bridging therapy to control disease burden prior to CAR-T cell treatment.

[0008] Chemotherapeutic drugs such as cyclophosphamide (Cy) and fludarabine (Flu) alone and/or in combination are the most commonly used lymphodepleting regimen in CAR-T cell therapy and are typically needed in order to make CAR-T therapy therapeutically effective. Moreover, CAR-T therapy complicates the manufacturing and/or introduction of genetically engineered products into the subject, making CAR-T approaches commercially unfavorable. Additionally, the introduction of genetically engineered CAR-T products to the subject has raised concerns about secondary malignancies. In November 2023, the FDA announced an investigation into several reported cases of secondary T cell malignancies, including CAR-positive lymphoma, in patients who previously received CAR-T cell therapy products. In January 2024, the FDA began requiring drugmakers to add a safety label warning to CAR-T cell products. These and other logistical issues make the use of the CAR-T approach to treating autoimmune disorders impractical and unrealistic.

[0009] Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation and joint damage, driven in part by the dysregulation of B cells. B cells contribute to RA pathogenesis by producing autoantibodies (such as rheumatoid factor and anti-citrullinated protein antibodies), presenting antigens to T cells, and secreting pro-inflammatory cytokines. Targeting B cells has become a pivotal therapeutic strategy in RA, as evidenced by the efficacy of B-cell-depleting therapies like rituximab. By reducing autoantibody production and dampening immune activation, B-cell modulation helps control inflammation, slow disease progression, and improve clinical outcomes. This highlights the critical role of B cells in RA and the importance of therapies aimed at their regulation.

[0010] Treating RA presents several challenges. Disease progression and response to therapy vary widely among patients, requiring individualized treatment plans. Current treatments, such as disease-modifying antirheumatic drugs (DMARDs), biologics, and Janus kinase (JAK) inhibitors, aim to reduce inflammation, prevent joint damage, and improve symptoms. However, achieving sustained remission can be difficult, as many patients experience partial response or develop resistance over time. Additionally, the long-term use of these therapies carries risks of side effects, including immunosuppression, infections, and organ toxicity. Patient adherence to treatment, high costs of advanced therapies, and access to specialized care further complicate management.

[0011] Sjögren's disease (SjD), also known as Sjögren's and Sjögren's syndrome, is a chronic autoimmune disorder characterized by the immune system attacking the body's moisture-producing glands, leading to hallmark symptoms of dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia). Beyond these primary symptoms, the disease can also affect other organs, such as the kidneys, lungs, liver, and joints, causing systemic complications like fatigue, chronic pain, and inflammation. Sjögren's is often associated with other autoimmune conditions, such as rheumatoid arthritis or lupus, making diagnosis and management more complex. Its pathogenesis is driven by immune dysregulation, involving B-cell hyperactivity, T-cell-mediated inflammation, and autoantibody production, though the precise mechanisms remain incompletely understood.

[0012] Treating Sjögren's disease is challenging due to its variable presentation, lack of a cure, and limited targeted therapies. Current treatments focus on symptom management rather than addressing the underlying autoimmune processes. Artificial tears, saliva substitutes, and medications like pilocarpine and cevimeline are commonly used to alleviate dryness, but they provide only partial relief for many patients. Systemic therapies, such as immunosuppressants or biologics, have shown mixed efficacy and are often reserved for severe, systemic cases. Additionally, the heterogeneity of the disease and difficulty in identifying reliable biomarkers complicate the development of novel therapies.

[0013] In view of the lack of existing therapies and the significant limitations of CAR-T approaches to treatment, there remains an unmet need for safe and effective treatment options for patients with SLE that can induce drug-free remissions. These challenges highlight the need for a better understanding of the disease mechanisms and more effective, personalized treatment strategies. The present invention provides a solution by using a CD19-based T cell engager for the treatment of SLE, RA, Sjögren's disease, and other autoimmune disorders.

BRIEF SUMMARY

[0014] Described herein, in certain embodiments, are methods for treating immune diseases and disorders using a multi-specific binding protein described herein.

[0015] One aspect of the disclosure is a method of treating an immune disorder characterized by B cell pathogenesis in a subject in need thereof, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising: a) a first

antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein: HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21.

[0016] One aspect of the disclosure is a method of achieving B cell depletion in a subject suffering from an autoimmune disease, wherein said method including subcutaneously administering to the subject a multi-specific binding protein comprising: a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21.

[0017] In an aspect, the immune disorder characterized by B cell pathogenesis, autoimmune disease, or autoimmune disorder is selected from the group consisting of SLE,

rheumatoid arthritis, multiple sclerosis, type 1 diabetes, adult dermatomyositis, sine myositis, juvenile dermatomyositis, Sjögren's disease, neuromyelitis optica spectrum disorder, myasthenia gravis, ANCA-positive vasculitis, antiphospholipid syndrome, autoimmune cytopenias, autoimmune encephalitis, and pemphigus vulgaris.

[0018] One aspect of the disclosure is a method of treating SLE in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising: a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein: HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein: HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21.

[0019] One aspect of the disclosure is a method of treating RA in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising: a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein: HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein: HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO:

16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21.

[0020] One aspect of the disclosure is method of treating Sjögren's disease in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising: a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein: HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein: HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21.

[0021] In an aspect, the multi-specific binding protein further includes a third antigen-binding site that binds to human serum albumin comprising heavy chain complementarity determining regions (HCDR) wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 25 or 26, HCDR2 comprises the amino acid sequence of SEQ ID NO: 27, and HCDR3 comprises the amino acid sequence of SEQ ID NO: 28 or 29.

[0022] One aspect of the disclosure is a method of treating an immune disorder characterized by B cell pathogenesis in a subject in need thereof, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising: a) a first antigen-binding site that binds to CD19 comprising a heavy chain variable domain (VH) comprising an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 1 and a light chain variable domain (VL) comprising an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 2; and b) a second antigen-binding site that binds to human CD3 comprising a VH comprising an amino acid sequence at

least about 80% identical to the amino acid sequence of SEQ ID NO: 12 and a VL comprising an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 13.

[0023] One aspect of the disclosure is a method of achieving B cell depletion in a subject suffering from an autoimmune disease, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising: a) a first antigen-binding site that binds to CD19 comprising a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 1 and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 2; and b) a second antigen-binding site that binds to human CD3 comprising a VH comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 12 and a VL comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 13.

[0024] One aspect of the disclosure is a method of treating SLE in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising: a) a first antigen-binding site that binds to CD19 comprising a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 1 and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 2; and b) a second antigen-binding site that binds to human CD3 comprising a VH comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 12 and a VL comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 13.

[0025] One aspect of the disclosure is a method of treating RA in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising: a) a first antigen-binding site that binds to CD19 comprising a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 1 and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 2; and b) a second antigen-binding site that binds to human CD3 comprising a VH comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 12 and a VL

comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 13.

[0026] One aspect of the disclosure is a method of treating Sjögren's disease in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising: a) a first antigen-binding site that binds to CD19 comprising a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 1 and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 2; and b) a second antigen-binding site that binds to human CD3 comprising a VH comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 12 and a VL comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 13.

[0027] In an aspect, the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH

comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 1; or alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 1.

[0028] In an aspect, the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL

comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 2; or alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO:2.

[0029] In an aspect, the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 12; or alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 12.

[0030] In an aspect, the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 13; or alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO:13.

[0031] In an aspect, the multi-specific binding protein further includes a third antigen-binding site that binds to human serum albumin (HSA) comprising a VH comprising an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 24.

[0032] In an aspect, the VH comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 24; or alternatively the VH comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 24.

[0033] One aspect of the disclosure is a method of treating an immune disorder characterized by B cell pathogenesis in a subject in need thereof, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 41.

[0034] One aspect of the disclosure is a method of achieving B cell depletion in a subject suffering from an autoimmune disease, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 41.

[0035] One aspect of the disclosure is method of treating SLE in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 41.

[0036] In an aspect, the subject has not received (i) Cellular therapy (CAR T) or gene therapy product directed at any target, (ii) Any anti-CD19 or anti-CD20 therapy, (iii) Inhibitors of JAK, Bruton tyrosine kinase, or tyrosine kinase 2, (iv) Tacrolimus, cyclosporin, voclosporin, azathioprine, or mycophenolic acid and its derivatives, or (v) Cyclophosphamide or a biologic therapy prior to the administration of the multi-specific binding protein.

[0037] One aspect of the disclosure is a method of treating RA in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 41.

[0038] One aspect of the disclosure is a method of treating Sjögren's disease in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 41.

[0039] In an aspect, the subject has not received (i) Cellular therapy (CAR T) or gene therapy product directed at any target, (ii) Any anti-CD19 or anti-CD20 therapy, (iii) Non-biologic DMARD or (iv) Cyclophosphamide or a biologic therapy prior to the administration of the multi-specific binding protein.

[0040] In an aspect, the subject has received leflunomide cholestyramine, glucocorticoids, antimalarials, or sialagogues prior to the administration of said multi-specific binding protein.

[0041] In an aspect, wherein after administration of said multi-specific binding protein, the subject has an achievement of disease response. In an aspect, the achievement of disease response is a decrease in ESSDAI $\geq$ 3 (MCII), decrease in ESSPRI $\geq$ 1 or 15% (MCII), a ESSDAI $<$ 5, or an ESSDAI equal to 0.

[0042] In an aspect, the multi-specific binding protein comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 92% identical

to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 41; or alternatively the multi-specific binding protein comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 41.

[0043] In an aspect, the first antigen-binding site comprises an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about

97% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 11; or alternatively the first antigen-binding site comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 11.

[0044] In an aspect, the second antigen-binding site comprises an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 22 or 23; or alternatively the second antigen-binding site comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 22 or 23.

[0045] In an aspect, the first antigen-binding site and/or the second antigen-binding site comprise a single-chain variable fragment (scFv). In an aspect, the third antigen-binding site comprises a single-domain antibody (sdAb). In an aspect, the multi-specific binding protein comprises a single polypeptide chain.

[0046] In an aspect, the multi-specific binding protein comprises a single polypeptide chain and the third antigen-binding site is positioned N-terminal to both the first antigen-binding site and the second antigen-binding site in the polypeptide chain; or wherein the third antigen-binding site is positioned N-terminal to the first antigen-binding site, and the first antigen-binding site is positioned N-terminal to the second antigen-binding site in the polypeptide chain; or wherein the third antigen-binding site is positioned N-terminal to the second antigen-binding site, and the second antigen-binding site is positioned N-terminal to the first antigen-binding site in the polypeptide chain.

[0047] In an aspect, the multi-specific binding protein comprises a single polypeptide chain and the third antigen-binding site is positioned C-terminal to both the first antigen-binding site and the second antigen-binding site in the polypeptide chain; or wherein the first antigen-binding site is positioned N-terminal to the second antigen-binding site, and the second antigen-binding site is positioned N-terminal to the third antigen-binding site in the polypeptide chain; or wherein the second antigen-binding site is positioned N-terminal to the first antigen-binding site, and the first antigen-binding site is positioned N-terminal of the third antigen-binding site in the polypeptide chain.

[0048] In an aspect, the multi-specific binding protein comprises a single polypeptide chain and the first antigen-binding site is positioned N-terminal to the third antigen-binding site, and the third antigen-binding site is positioned N-terminal to the second antigen-binding site in the polypeptide chain; or wherein the second antigen-binding site is positioned N-terminal to the third antigen-binding site, and the third antigen-binding site is positioned N-terminal binding protein the first antigen-binding site in the polypeptide chain.

[0049] In an aspect, the administration of said multi-specific binding protein produces B cell depletion in said subject within 96 hours of administration of said multi-specific binding protein.

[0050] In an aspect, the administration of said multi-specific binding protein produces a persistent B cell depletion that is sustained to at least 90 days after administration of said multi-specific binding protein.

[0051] In an aspect, the administration of said multi-specific binding protein produces a deep and/ or sustained B cell depletion in tissue.

[0052] In an aspect, the tissue is selected from the group consisting of bone marrow tissue, spleen tissue, axial lymph node tissue, and mandibular lymph node tissue.

[0053] In an aspect, the administration of said multi-specific binding protein produces at least about a 75% reduction in peripheral blood B cells. In an aspect, the administration of said multi-specific binding protein produces at least about a 95% reduction in peripheral blood B cells.

[0054] In an aspect, the subject is administered a dose of at least 10μg said multi-specific binding protein. In an aspect, the subject is administered a dose of at least 20μg said multi-specific binding protein. In an aspect, the subject is administered a dose of at least 30μg said multi-specific binding protein. In an aspect, the subject is administered a dose of at least 40μg said multi-specific binding protein. In an aspect, the subject is administered a dose of at least 50μg said multi-specific binding protein. In an aspect, the subject is administered a dose of at least 60μg said multi-specific binding protein.

[0055] In an aspect, the subject is administered at least an initial dose and at least one target dose. In an aspect, the target dose is at least about 2xs greater than the initial dose; alternative the target dose at least about 2.5xs greater than the initial dose; alternatively the target dose is at least about 3xs greater than the initial dose; alternatively the target dose is at least about 3.5xs greater than the initial dose; alternatively the target dose is at least about 4xs greater than the initial dose; alternatively the target dose is at least about 4.5xs greater than the initial dose; alternatively the target dose is at least about 5xs greater than the initial dose; alternatively the target dose is at least about 5.5xs greater than the initial dose; alternatively the target dose is at least about 6xs greater than the initial dose; alternatively the target dose is at least about 6.5xs greater than the initial dose; alternatively the target dose is at least about 7xs greater than the initial dose; alternatively the target dose is at least about 7.5xs greater than the initial dose; alternatively the target dose is at least about 8xs greater than the initial dose; alternatively the target dose is at least about 8.5xs greater than the initial dose; alternatively the target dose is at least about 9xs greater than the initial dose; alternatively the target dose is at least about 9.5xs greater than the initial dose;

alternatively the target dose is at least about 10xs greater than the initial dose; or alternatively the target dose is at least about 10.5xs greater than the initial dose.

[0056] One aspect of the disclosure is a therapeutic composition comprising a polynucleotide encoding a multi-specific binding protein, wherein the polynucleotide comprises at least about 70% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42 or SEQ ID NO: 43.

[0057] In an aspect, the polynucleotide comprises at least about 80% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 85% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 88% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 90% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 91% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 92% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 93% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 94% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 95% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 96% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 97% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 98% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 99% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; or alternatively the polynucleotide comprises at least about 100% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42.

[0058] In an aspect, the polynucleotide comprises at least about 80% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 85% nucleic acid sequence identity to the nucleic acid sequence of SEQ

ID NO: 43; alternatively the polynucleotide comprises at least about 88% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 90% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 91% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 92% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 93% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 94% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 95% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 96% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 97% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 98% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 99% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; or alternatively the polynucleotide comprises at least about 100% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43.

[0059] In an aspect, the polynucleotide encode a multi-specific binding protein, wherein the multi-specific binding protein comprises an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 41 or SEQ ID NO: 44.

[0060] In an aspect, the multi-specific binding protein comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein

comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 41; or alternatively the multi-specific binding protein comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 41.

[0061] In an aspect, the multi-specific binding protein comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 98% identical

to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 44; or alternatively the multi-specific binding protein comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 44.

[0062] In an aspect, the polynucleotide is formulated and/or in communication with a delivery vehicle. In an aspect, the polynucleotide is at least partially encapsulated with a delivery vehicle. In an aspect, the delivery vehicle is selected from the group consisting of amphipathic molecules, amino-lipidated peptides, tertiary amino lipidated cationic peptides, a cationic component, a peptoid, a lipoid, a liposome, a lipoplex, a lipid nanoparticle, a cationic lipid nanoparticle, a polymeric compound, and a conjugate.

[0063] In an aspect, the therapeutic composition is configured to be administered subcutaneously.

[0064] In an aspect, the composition is configured to be administered to a subject know to have or suspected to have an autoimmune disease. In an aspect, the autoimmune disease is selected from the group consisting of SLE, rheumatoid arthritis, multiple sclerosis, type 1 diabetes, adult dermatomyositis, sine myositis, juvenile dermatomyositis, Sjögren's disease, neuromyelitis optica spectrum disorder, myasthenia gravis, ANCA-positive vasculitis, antiphospholipid syndrome, autoimmune cytopenias, autoimmune encephalitis, and pemphigus vulgaris.

[0065] In an aspect, the composition further includes one or more one or more therapeutically acceptable carriers, therapeutically acceptable diluents, therapeutically acceptable excipients or other therapeutic agents.

[0066] In an aspect, the therapeutically acceptable excipients are selected from the group consisting of salts, buffering agents, preservatives, antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes, emollients, emulsifiers, fillers, film formers, coatings, flavors, fragrances, glidants, lubricants, sorbents, suspending or dispersing agents, sweeteners, and waters of hydration.

[0067] One aspect of the disclosure is a method of treating an immune disorder characterized by B cell pathogenesis in a subject or a method of achieving B cell depletion in a subject suffering from an autoimmune disease, comprising administering a therapeutically effective amount of the therapeutic composition of any one of embodiments to the subject.

[0068] One aspect of the disclosure is a method of treating SLE in a subject, comprising administering a therapeutically effective amount of the therapeutic composition of any one of embodiments to the subject.

[0069] One aspect of the disclosure is a method of treating RA in a subject, comprising administering a therapeutically effective amount of the therapeutic composition of any one of embodiments to the subject.

[0070] One aspect of the disclosure is a method of treating Sjögren's disease in a subject, comprising administering a therapeutically effective amount of the therapeutic composition of any one of embodiments to the subject.

[0071] One aspect of the disclosure is a kit comprising the therapeutic composition of any one of embodiments and instructions for use.

[0072] In an aspect, the instructions for use include instructions for subcutaneous administration.

[0073] One aspect of the disclosure include the use of a multi-specific binding protein comprising: a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein: HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein: HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21 in the manufacturer of a medicament for treating an immune disorder characterized by B cell pathogenesis in a subject or a method of achieving B cell depletion in a subject suffering from an autoimmune disease.

[0074] In an aspect, the immune disorder characterized by B cell pathogenesis or the autoimmune disease is selected from the group consisting of SLE, rheumatoid arthritis, multiple

sclerosis, type 1 diabetes, adult dermatomyositis, sine myositis, juvenile dermatomyositis, Sjögren's disease, neuromyelitis optica spectrum disorder, myasthenia gravis, ANCA-positive vasculitis, antiphospholipid syndrome, autoimmune cytopenias, autoimmune encephalitis, and pemphigus vulgaris.

[0075] One aspect of the disclosure include the use of a multi-specific binding protein comprising: a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein: HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein: HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21 in the manufacturer of a medicament for treating SLE in a subject in need thereof.

[0076] One aspect of the disclosure include the use of a multi-specific binding protein comprising: a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein: HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein: HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the

amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21 in the manufacturer of a medicament for treating RA in a subject in need thereof.

[0077] One aspect of the disclosure include the use of a multi-specific binding protein comprising: a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein: HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein: HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21 in the manufacturer of a medicament for treating Sjögren's disease in a subject in need thereof.

[0078] In an aspect, the multi-specific binding protein further includes a third antigen-binding site that binds to human serum albumin comprising heavy chain complementarity determining regions (HCDR) wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 25 or 26, HCDR2 comprises the amino acid sequence of SEQ ID NO: 27, and HCDR3 comprises the amino acid sequence of SEQ ID NO: 28 or 29.

[0079] These and other advantages, aspects, and novel features of the present disclosure, as well as details of illustrated embodiments thereof, will be more fully understood from the following description and drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0080] Various aspects of the present disclosure will now be described, by way of example only, with reference to the attached Figures, wherein:

[0081] **FIG. 1** is a study Design for the treatment of SLE with CLN-978 according to an aspect of this disclosure.

[0082] **FIG. 2** is a treatment Plan for monitoring the effects of CLN-978 in subjects with SLE according to an aspect of this disclosure.

[0083] **FIG. 3** is a schematic drawing of CLN-978.

[0084] **FIG. 4** is a graph showing CLN-978 produces an effective and sustained depletion of peripheral B-cells.

[0085] **FIG. 5** is a graph showing preliminary clinical pharmacokinetics (PK) for CLN-978 overlayed with a simulated PK from a preclinical PK model.

[0086] **FIGs. 6A-6F** are graphs showing B-cell depletion, T-cell activation, and cytokine analysis in a subject treated with CLN-978.

[0087] **FIG. 7** is a table summarizing the clinical observations from three patients treated with 30 μg of CLN-978 administered subcutaneously weekly.

[0088] **FIG. 8** shows images from a patient treated with 30 μg of CLN-978 administered subcutaneously once per week showing response to the CLN-978 treatment.

[0089] **FIG. 9** is an illustration of a systems pharmacology model diagram.

[0090] **FIGs. 10A** and **10B** are graphs showing projected B-cell depletion after a single dose of 30 μg SC. **FIG. 10A** is a graph for scenario one and **FIG. 10B** is a graph for scenario 2. Dashed black line = 4 cells/μL. In both cases, the minimum number of B cells in circulation is 1.7 cells/μL.

[0091] **FIGs. 11A** and **11B** are graphs showing projected B-cell depletion after administration of possible dose levels 1 through 4. DL1 = Day 1- 10 μg, Day 8 – 10 μg; DL2 = Day 1- 10 μg, Day 8 – 20 μg; DL3 = Day 1 – 10 μg, Day 8 30 μg; DL4 = Day 1 – 10 μg, Day 8 – 10 μg, Day 15 – 30 μg, and Day 22 – 30 μg. Scenario 1 (**FIG. 11A**) and Scenario 2 (**FIG. 11B**). Dashed black line = 4 cells/μL.

[0092] **FIGs. 12A-12C** are graphs depicting *in vitro* activity in PBMCs from healthy donors and patients with SLE or RA. **FIG. 12A** shows T-cell activation in CD4+ CD25+ (left) or CD8+ CD25+ (right). **FIG. 12B** shows B-cell depletion. **FIG. 12C** shows cytokine release (IFN-γ, left; TNF-α, right).

[0093] **FIG. 13** shows the quantification of peripheral B cells after administration of CLN-978 to cynomolgus monkeys.

[0094] **FIG. 14** shows deep B-cell depletion in cynomolgus monkey tissue after four weekly SC doses of CLN-978.

[0095] **FIG. 15** is a table showing the selectivity of a PK assay in normal and SLE sera.

[0096] **FIG. 16** is a graph depicting pharmacokinetics of CLN-978 following subcutaneous administration in cynomolgus monkeys.

[0097] **FIGs. 17A** and **17B** are graphs depicting pharmacodynamics (B cell) of CLN-978 in cynomolgus monkeys on an individual (± SD) linear scale (**FIG. 17A**) and Mean (± SD) linear scale (**FIG. 17B**).

[0098] **FIG. 18** is a graph showing how human PK/model predicts B cell depletion in NHL Patients.

[0099] **FIGs. 19A** and **19B** are graphs showing dose-related tissue B cell depletion observed in cynomolgus monkeys.

[0100] **FIGs. 20A** and **20B** are graphs showing that deep and sustained peripheral blood and bone marrow B cell depletion was observed in a single cynomolgus monkey (Animal 4502).

DETAILED DESCRIPTION

[0101] **Introduction**

[0102] The present invention is directed toward addressing the unmet need for safe and effective treatment options for patients with SLE and other autoimmune disorders that can induce drug-free remissions (van Vollenhoven, 2021). More specifically, the present invention provides an exemplary bispecific T cell engaging (TCE) antibody, CLN-978, in SLE based on the potential of this TCE for a potent depletion of tissue-resident B cell populations resulting in durable remissions for patients with moderate to severe SLE.

[0103] Bispecific T cell engaging (TCE) antibodies targeting B cell surface antigens provide an alternative means of delivering T cell redirecting therapy that has shown similar potential to induce deep depletion of both normal and malignant B cells in patients with B cell acute lymphoblastic leukemia and non-Hodgkin lymphoma (Tian, 2021). Deep and durable responses in patients with various B cell malignancies suggest that the TCE approach can induce similarly potent depletion of tissue-resident B cell populations. Several ongoing studies are assessing CD20-directed TCEs as a treatment for SLE (NCT05155345, NCT06041568), but the

CD-19 target provides theoretical advantages through broader coverage of the B cell compartment, including pro-B cells, plasmablasts, and plasma cells (Zhang, 2023).

[0104] CLN-978 is a CD19xCD3 T cell engager designed with an extended serum half-life. Preclinically, CLN-978 can effectively redirect T cells to kill CD19-expressing tumor cells in vitro and in vivo in both the peripheral blood and tissues, including cells with low levels of CD19 expression. The molecule is currently under study as a novel therapy for patients with B cell malignancies (NCT05879744), which commenced in 2023. Initial clinical experience from that trial supports pre-clinical studies demonstrating that a fixed duration of CLN-978 treatment can achieve rapid and deep B cell depletion with acceptable safety.

[0105] In the present investigation, the inventors describe an open-label evaluation of the safety and tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of subcutaneously (SC)-administered CLN-978 for the treatment of active Systemic Lupus Erythematosus (SLE). This clinical trial is an exploratory study designed to yield preliminary data about the safety, clinical, and biologic efficacy of CLN-978 in SLE patients. SLE is a classic B-cell-mediated autoimmune disease, while rheumatoid arthritis and type 1 diabetes were initially considered to be predominantly T-cell mediated. However, recent studies suggest a role of B cells in the pathogenesis of these autoimmune diseases. As such, the data from the use of CLN-978 in SLE may be used to inform the treatment of other autoimmune diseases in which B cells are implicated, including but not limited to rheumatoid arthritis, multiple sclerosis, type 1 diabetes, adult dermatomyositis, sine myositis, juvenile dermatomyositis, Sjögren's disease, neuromyelitis optica spectrum disorder, myasthenia gravis, systemic sclerosis, IgA nephropathy, ANCA-positive vasculitis, antiphospholipid syndrome, autoimmune cytopenias, autoimmune encephalitis, pemphigus vulgaris.

[0106] To facilitate an understanding of the present disclosure, a number of terms and phrases are defined below.

[0107] **Definitions**

[0108] Unless otherwise defined, 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 methods described herein belong. Any reference to standard methods refers to the most recent available version of the method at the time of filing of this disclosure unless otherwise indicated.

[0109] For any method disclosed herein that includes discrete steps, the steps may be conducted in any feasible order. And, as appropriate, any combination of two or more steps may be conducted simultaneously.

[0110] All headings are for the convenience of the reader and should not be used to limit the meaning of the text that follows the heading, unless so specified.

[0111] The words "preferred" and "preferably" refer to embodiments of the invention that may afford certain benefits, under certain circumstances. However, other embodiments may also be preferred, under the same or other circumstances. Furthermore, the recitation of one or more preferred embodiments does not imply that other embodiments are not useful and is not intended to exclude other embodiments from the scope of the invention.

[0112] The term "comprises" and variations thereof do not have a limiting meaning where these terms appear in the description and claims. Such terms will be understood to imply the inclusion of a stated step or element or group of steps or elements but not the exclusion of any other step or element or group of steps or elements.

[0113] By "consisting of" is meant including, and limited to, whatever follows the phrase "consisting of." Thus, the phrase "consisting of" indicates that the listed elements are required or mandatory, and that no other elements may be present. By "consisting essentially of" is meant including any elements listed after the phrase, and limited to other elements that do not interfere with or contribute to the activity or action specified in the disclosure for the listed elements. Thus, the phrase "consisting essentially of" indicates that the listed elements are required or mandatory, but that other elements are optional and may or may not be present depending upon whether or not they materially affect the activity or action of the listed elements.

[0114] The singular form "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. These articles refer to one or to more than one (i.e., to at least one). As used herein, the term "or" is generally employed in its usual sense including "and/or" unless the content clearly dictates otherwise. The term "and/or" means any one or more of the items in the list joined by "and/or". As an example, "x and/or y" means any element of the three-element set {(x), (y), (x, y)}. In other words, "x and/or y" means "one or both of x and y". As another example, "x, y, and/or z" means any element of the seven-element set {(x), (y), (z), (x, y), (x, z), (y, z), (x, y, z)}. In other words, "x, y and/or z" means "one or more of x, y and z".

[0115] Where ranges are given, endpoints include all numbers subsumed within that range (e.g., 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, 5, etc.). Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or subrange within the stated ranges in different embodiments of the disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise. Herein, "up to" a number (for example, up to 50) includes the number (for example, 50). The term "in the range" or "within a range" (and similar statements) includes the endpoints of the stated range.

[0116] Reference throughout this specification to "one aspect," "an aspect," "certain aspects," or "some aspects," etc., means that a particular feature, configuration, composition, or characteristic described in connection with the aspect is included in at least one aspect of the disclosure. Thus, the appearances of such phrases in various places throughout this specification are not necessarily referring to the same embodiment of the disclosure. Furthermore, the particular features, configurations, compositions, or characteristics may be combined in any suitable manner in one or more aspects.

[0117] Unless otherwise indicated, all numbers expressing quantities of components, molecular weights, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." As used herein in connection with a measured quantity, the term "about" refers to that variation in the measured quantity as would be expected by the skilled artisan making the measurement and exercising a level of care commensurate with the objective of the measurement and the precision of the measuring equipment used. The term "about" as used in connection with a numerical value throughout the specification and the claims denotes an interval of accuracy, familiar and acceptable to a person skilled in the art. In general, such interval of accuracy is +/-10%. Accordingly, unless otherwise indicated to the contrary, the numerical parameters set forth in the specification and claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention. At the very least, and not as an attempt to limit the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[0118] Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples

are reported as precisely as possible. All numerical values, however, inherently contain a range necessarily resulting from the standard deviation found in their respective testing measurements.

[0119] The term "exemplary" means serving as a non-limiting example, instance, or illustration. As utilized herein, the terms "e.g.," and "for example" set off lists of one or more non-limiting aspects, examples, instances, or illustrations.

[0120] As used herein, the term "substantially" refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. Biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term "substantially" is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena. For example, "substantially" may refer to being within at least about 20%, alternatively at least about 10%, alternatively at least about 5% of a characteristic or property of interest.

[0121] The term “multi-specific binding protein” refers to a protein or protein conjugate capable of binding two or more different targets (e.g., two or more different antigens or two or more different epitopes of the same antigen). For example, the multi-specific binding protein can bind two or more different targets through two or more different binding domains. The structure and/or function of the multi-specific binding protein can be based on the structure and/or function of an antibody, e.g., a full-length or whole immunoglobulin molecule, an antibody heavy chain variable domain (VH) and/or light chain variable domain (VL), and/or a single chain antibody. In one example, each one of the binding domains of a multi-specific binding protein according to the disclosure comprises the minimum structural requirements of an antibody, which allow for the target binding. This minimum requirement may be, e.g., defined by the presence of at least the three heavy chain CDRs (i.e., CDR1, CDR2, and CDR3 of the VH domain) and/or the three light chain CDRs (i.e., CDR1, CDR2 and CDR3 of the VL domain). An alternative approach to defining the minimal structural requirements of an antibody is defining the epitope of a specific target to which the antibody binds, or by referring to a known antibody with which the antibody competes to bind to the same epitope that the known antibody binds. The antibodies on which the constructs according to the disclosure are based include, for example, monoclonal, recombinant, chimeric, deimmunized, humanized, and human antibodies.

[0122] Any one of the binding domains of a multi-specific binding protein, according to the disclosure, may comprise the above referred groups of CDRs. Those CDRs may be comprised

in the framework of a VH and/or VL. Fd fragments, for example, have two VH domains and often retain some antigen-binding function of the intact antigen-binding domain. Additional examples for formats of antibody fragments, antibody variants or binding domains include: (1) a Fab fragment, a monovalent fragment having the VL, VH, CL and CH1 domains; (2) a F(ab')2 fragment, a bivalent fragment having two Fab fragments linked by a disulfide bridge at the hinge region; (3) an Fd fragment having the two VH and CH1 domains; (4) an Fv fragment having the VL and VH domains of a single arm of an antibody; (5) a dAb fragment (Ward et al., (1989) Nature 341:544-546), which has a VH domain; (6) an isolated complementarity determining region (CDR); and (7) a single chain Fv (scFv), which may be derived, for example, from an scFv-library.

[0123] Multi-specific binding proteins according to the disclosure may also comprise modified fragments of antibodies, also called antibody variants, such as di-scFv or bi(s)-scFv, scFv-Fc, scFv-zipper, scFab, Fab2, Fab3, diabodies, single chain diabodies, tandem diabodies (Tandab's), tandem di-scFv, tandem tri-scFv, "multibodies" such as triabodies or tetrabodies, or single-domain antibodies such as nanobodies or single variable domain antibodies comprising a single variable domain, which might be VH (also called VHH in the context of an sdAb) or VL, that specifically bind an antigen or epitope independently of other V regions or domains.

[0124] As used herein, the terms "single-chain Fv," "single-chain antibody," and "scFv" refer to a single-polypeptide-chain antibody fragment that comprise the variable regions from both the heavy and light chains but lack the constant regions. Generally, a single-chain antibody further comprises a peptide linker connecting the VH and VL domains which enables it to form the desired structure to bind to antigen. In specific embodiments, single-chain antibodies can also be bispecific, multispecific, human, humanized and/or synthetic.

[0125] Furthermore, the "multi-specific binding protein" described herein can be a monovalent, bivalent or polyvalent/multivalent construct. Moreover, the "multi-specific binding protein" described herein can include a molecule consisting of only one polypeptide chain, or a molecules consisting of more than one polypeptide chain, wherein the chains can be either identical (homodimers, homotrimers or homo oligomers) or different (heterodimer, heterotrimer or heterooligomer).

[0126] The domains of the multi-specific binding protein of the present disclosure may be connected through one or more peptide bonds and/or peptide linkers. The term "peptide linker"

comprises in accordance with the present disclosure an amino acid sequence linking two domains. The peptide linkers can also be used to fuse the third domain to the other domains of the multi-specific binding protein of the disclosure. An essential technical feature of such peptide linker is that it does not comprise any polymerization activity.

[0127] The term "binding domain" or "domain that binds (an antigen)" characterizes in connection with the present disclosure a domain which (specifically) binds to or interacts with a given target epitope or a given target side on the target molecules (antigens), e.g. CD19, serum albumin, and CD3, respectively. The structure and function of the first binding domain, the second binding domain, and/or the third binding domain can be based on the structure and/or function of an antibody, e.g. of a full-length or whole immunoglobulin molecule. A binding domain can be drawn from the VH and/or VL or VHH domain of an antibody or fragment thereof. For example, a binding domain can include three light chain CDRs (i.e., CDR1, CDR2 and CDR3 of the VL domain) and/or three heavy chain CDRs (i.e., CDR1, CDR2 and CDR3 of the VH domain). A binding domain can also include VHH CDRs (i.e., CDR1, CDR2 and CDR3 of the VHH region).

[0128] The terms "variable domain" and "variable region" are used interchangeably and refer to the portions of the antibody or immunoglobulin domains that exhibit variability in their sequence and that are involved in determining the specificity and binding affinity of a particular antibody. Variability is not evenly distributed throughout the variable domains of antibodies; it is concentrated in sub-domains of each of the heavy and light chain variable regions. These sub-domains are called "hypervariable regions" or "complementarity determining regions" (CDRs). The more conserved (i.e., non-hypervariable) portions of the variable domains are called the "framework" regions (FRM or FR) and provide a scaffold for the six CDRs in three-dimensional space to form an antigen-binding surface.

[0129] In the present disclosure, any one of the binding domains of the multi-specific binding protein may comprise a single domain antibody (sdAb). A single domain antibody comprises a single, monomeric antibody variable domain which is able to bind selectively to a specific antigen, independently of other variable regions or domains. The first single domain antibodies were engineered from heavy chain antibodies found in camelids, and these are called VHH fragments. Cartilaginous fishes also have heavy chain antibodies (IgNAR) from which single domain antibodies called VNAR fragments can be obtained. An alternative approach is to split the dimeric variable domains from common immunoglobulins e.g., from humans or rodents

into monomers, hence obtaining VH or VL as a single domain antibody. Although most research into single domain antibodies is currently based on heavy chain variable domains, nanobodies derived from light chains have also been shown to bind specifically to target epitopes. Examples of single domain antibodies include nanobodies and single variable domain antibodies.

[0130] As used herein, the term "antigen-binding site" refers to the part of an immunoglobulin molecule or a derivative or variant thereof that participates in antigen binding. In human antibodies, the antigen binding site is formed by amino acid residues of the N-terminal variable ("V") regions of the heavy ("H") and light ("L") chains. Three highly divergent stretches within the V regions of the heavy and light chains are referred to as "hypervariable regions" which are interposed between more conserved flanking stretches known as "framework regions," or "FR." Thus the term "FR" refers to amino acid sequences which are naturally found between and adjacent to hypervariable regions in immunoglobulins. In a human antibody molecule, the three hypervariable regions of a light chain and the three hypervariable regions of a heavy chain are disposed relative to each other in three dimensional space to form an antigen-binding surface. The antigen-binding surface is complementary to the three-dimensional surface of a bound antigen, and the three hypervariable regions of each of the heavy and light chains are referred to as "complementarity-determining regions," or "CDRs." In certain animals, such as camels and cartilaginous fish, the antigen-binding site is formed by a single antibody chain providing a "single domain antibody." Antigen-binding sites can exist in an intact antibody, in an antigen-binding fragment of an antibody that retains the antigen-binding surface, or in a recombinant polypeptide such as an scFv, using a peptide linker to connect the heavy chain variable domain to the light chain variable domain in a single polypeptide.

[0131] As used herein, the term "antibody" refers to a protein or a protein conjugate that comprises an antigen-binding site. An antibody can be monospecific or multi-specific (e.g., bispecific).

[0132] The terms "recipient", "individual", "subject", "host", and "patient", are used interchangeably herein and in some embodiments, refer to any mammalian subject for whom diagnosis, treatment, or therapy is desired, particularly humans. "Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and laboratory, zoo, sports, or pet animals, such as dogs, horses, cats, cows, sheep, goats,

pigs, mice, rats, rabbits, guinea pigs, monkeys etc. In some embodiments, the mammal is human. None of these terms require the supervision of medical personnel.

[0133] As used herein, the term "effective amount" refers to the amount of a compound (e.g., a compound of the present disclosure) sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications or dosages and is not intended to be limited to a particular formulation or administration route. As used herein, the term "treating" includes any effect, e.g., lessening, reducing, modulating, ameliorating or eliminating, that results in the improvement of the condition, disease, disorder, and the like, or ameliorating a symptom thereof.

[0134] As used herein, the term "pharmaceutical composition" refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use in vivo or ex vivo.

[0135] As used herein, the term "pharmaceutically acceptable carrier" refers to any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, emulsions (e.g., such as an oil/water or water/oil emulsions), and various types of wetting agents. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants, see e.g., Martin, Remington's Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, PA (1975).

[0136] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions of the present disclosure that consist essentially of, or consist of, the recited components, and that there are processes and methods according to the present disclosure that consist essentially of, or consist of, the recited processing steps.

[0137] The terms "nucleic acid sequence," "nucleotide sequence," or "polynucleotide sequence" are used interchangeably and refer to a continuous nucleic acid sequence. The sequence can be either single stranded or double stranded DNA or RNA, e.g., an mRNA.

[0138] The term "nucleic acid," in its broadest sense, includes any compound and/or substance that comprises a polymer of nucleotides. These polymers are often referred to as polynucleotides. Example nucleic acids or polynucleotides of the disclosure include, but are not limited to, ribonucleic acids (RNAs) or deoxyribonucleic acids (DNAs).

[0139] The phrase "nucleotide sequence encoding" or "encoding" refers to the nucleic acid (e.g., an mRNA or DNA molecule) coding sequence that encodes a polypeptide. As used herein, the terms "coding region" and "coding sequence", refer to an Open Reading Frame (ORF) in a polynucleotide that upon expression, yields a polypeptide or protein. The coding sequence can further include initiation and termination signals operably linked to regulatory elements, including a promoter and polyadenylation signal capable of directing expression in the cells of an individual or mammal to which the nucleic acid is administered. The coding sequence can further include sequences that encode signal peptides.

[0140] The term "polynucleotide" as used herein refers to polymers of nucleotides of any length, including ribonucleotides, deoxyribonucleotides, analogs thereof, or mixtures thereof. Aspects of this disclosure include compositions including polynucleotides having a length of 18-25 nucleotides (e.g., 18-mers, 19-mers, 20-mers, 21-mers, 22-mers, 23-mers, 24-mers, or 25-mers), or medium-length polynucleotides having a length of 26 or more nucleotides (e.g., polynucleotides of 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, about 65, about 70, about 75, about 80, about 85, about 90, about 95, about 100, about 110, about 120, about 130, about 140, about 150, about 160, about 170, about 180, about 190, about 200, about 210, about 220, about 230, about 240, about 250, about 260, about 270, about 280, about 290, or about 300 nucleotides), or long polynucleotides having a length greater than about 300 nucleotides (e.g., polynucleotides of between about 300 to about 400 nucleotides, between about 400 to about 500 nucleotides, between about 500 to about 600 nucleotides, between about 600 to about 700 nucleotides, between about 700 to about 800 nucleotides, between about 800 to about 900 nucleotides, between about 900 to about 1000 nucleotides, between about 300 to about 500 nucleotides, between about 300 to about 600 nucleotides, between about 300 to about 700 nucleotides, between about 300 to about 800 nucleotides, between about 300 to about 900 nucleotides, or about 1000 nucleotides in length, or even greater than about 1000 nucleotides in length.

[0141] Where a polynucleotide is double-stranded, its length may be similarly described in terms of base pairs. This term refers to the primary structure of the molecule. Thus, the term includes triple-, double- and single-stranded deoxyribonucleic acid ("DNA"), as well as triple-, double- and single-stranded ribonucleic acid ("RNA"). More particularly, the term "polynucleotide" includes polydeoxyribonucleotides (containing 2-deoxy-D-ribose),

polyribonucleotides (containing D-ribose), including tRNA, rRNA, hRNA, siRNA, and mRNA, whether spliced or unspliced, any other type of polynucleotide which is an N- or C-glycoside of a purine or pyrimidine base, and other polymers containing normucleotidic backbones, for example, polyamide (e.g., peptide nucleic acids "PNAs") and polymorpholino polymers, and other synthetic sequence-specific nucleic acid polymers providing that the polymers contain nucleobases in a configuration which allows for base pairing and base stacking, such as is found in DNA and RNA. In particular aspects, the polynucleotide comprises an mRNA.

[0142] Nucleotides are referred to by their commonly accepted single-letter codes. Unless otherwise indicated, nucleic acids are written left to right in 5′ to 3′ orientation. Nucleotides are referred to herein by their commonly known one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Accordingly, A represents adenine, C represents cytosine, G represents guanine, T represents thymine, and U represents uracil.

[0143] The T bases in the codon maps disclosed herein are present in DNA, whereas the T bases may be replaced by U bases in corresponding RNAs. For example, a codon-nucleotide sequence disclosed herein in DNA form, e.g., a vector or an in vitro translation (IVT) template, may have its T bases transcribed as U based in its corresponding transcribed mRNA. In this respect, both codon-optimized DNA sequences (comprising T) and their corresponding RNA sequences (comprising U) are considered codon-optimized nucleotide sequences of the present disclosure. Equivalent codon-maps can be generated by replacing one or more bases with non-natural bases. Thus, e.g., a TTC codon (DNA map) may correspond to a UUC codon (RNA map), which in turn may correspond to a 'P'C codon (RNA map in which U has been replaced with pseudouridine).

[0144] Standard A-T and G-C base pairs form under conditions that allow the formation of hydrogen bonds between the N3-H and C4-oxy of thymidine and the N1 and C6-NH2, respectively, of adenosine and between the C2-oxy, N3, and C4-NH2, of cytidine and the C2-NH2, N′—H and C6-oxy, respectively, of guanosine. Thus, for example, guanosine (2-amino-6-oxy-9-β-D-ribofuranosyl-purine) can be modified to form isoguanosine (2-oxy-6-amino-9-β-D-ribofuranosyl-purine). Such modification results in a nucleoside base, which will no longer effectively form a standard base pair with cytosine. However, modification of cytosine (1-β-D-ribofuranosyl-2-oxy-4-amino-pyrimidine) to form isocytosine (1-β-D-ribofuranosyl-2-amino-4-

oxy-pyrimidine-) results in a modified nucleotide which will not effectively base pair with guanosine but will form a base pair with isoguanosine.

[0145] Usually RNA may be obtainable by transcription of a DNA sequence, e.g., inside a cell. In eukaryotic cells, transcription is typically performed inside the nucleus or the mitochondria. In vivo, transcription of DNA usually results in the so-called premature RNA (also called pre-mRNA, precursor mRNA or heterogeneous nuclear RNA) which has to be processed into so-called messenger RNA, usually abbreviated as mRNA. Processing of the premature RNA, e.g. in eukaryotic organisms, comprises a variety of different posttranscriptional modifications such as splicing, 5'-capping, polyadenylation, export from the nucleus or the mitochondria and the like. The sum of these processes is also called maturation of RNA. The mature messenger RNA usually provides the nucleotide sequence that may be translated into an amino acid sequence of a particular peptide or protein. Typically, a mature mRNA comprises a 5'-cap, optionally a 5′ untranslated region ("5'UTR"), an open reading frame, optionally a 3′ untranslated region ("3'UTR") and a poly(A) tail.

[0146] As used herein, the term “messenger RNA” (mRNA) refers to any polynucleotide that encodes a polypeptide of interest and is capable of being translated to produce the encoded polypeptide in vitro, in vivo, in situ, or ex vivo.

[0147] In addition to messenger RNA, several non-coding types of RNA exist which may be involved in regulation of transcription and/or translation, and immunostimulation. Within the present disclosure the term "RNA" further encompasses any type of single stranded (ssRNA) or double stranded RNA (dsRNA) molecule known in the art, such as viral RNA, retroviral RNA and replicon RNA, small interfering RNA (siRNA), antisense RNA (asRNA), circular RNA (circRNA), ribozymes, aptamers, riboswitches, immunostimulating/immunostimulatory RNA, transfer RNA (tRNA), ribosomal RNA (rRNA), small nuclear RNA (snRNA), small nucleolar RNA (snoRNA), microRNA (miRNA), and Piwi-interacting RNA (piRNA).

[0148] As used herein, a “therapeutic polynucleotide” refers to a polynucleotide (e.g., an mRNA) that may be part of a therapeutic polynucleotide composition for delivery to a subject to treat a symptom, disease, or condition in a subject; prevent a symptom, disease, or condition in a subject; or to improve or otherwise modify the subject’s health.

[0149] As used herein, a "therapeutic polynucleotide composition" (or "therapeutic composition" for short) may refer to a composition including one or more therapeutic polynucleotides (e.g., mRNA) encapsulated by a delivery vehicle, which composition may be administered to a subject in need thereof using any suitable administration routes, such as intratumoral, intramuscular, etc. injection. An example of a therapeutic polynucleotide composition is an mRNA (therapeutic) nanoparticle comprising at least one mRNA encapsulated by a delivery vehicle molecule. A therapeutic composition may be administered in an "effective amount". An "effective amount" includes a "therapeutically effective amount" and a "prophylactically effective amount." The term "therapeutically effective amount" refers to an amount effective in treating and/or ameliorating a disease or condition in a subject. The term "prophylactically effective amount" refers to an amount effective in preventing and/or substantially lessening the chances of a disease or condition in a subject.

[0150] As used herein, "delivery vehicle" refers to any substance that facilitates, at least in part, the in vivo, in vitro, or ex vivo delivery of a polynucleotide (e.g., therapeutic polynucleotide) to targeted cells or tissues. Referring to something as a delivery vehicle need not exclude the possibility of the delivery vehicle also having therapeutic effects. Some versions of a delivery vehicle may provide additional therapeutic effects. The term "DV" may also be used herein as a shorthand for "delivery vehicle." In some aspects, the mRNA for use in the delivery vehicle complexes herein comprise an mRNA comprising at least one region encoding a peptide (e.g., a polypeptide), or protein, or functional fragment of the foregoing. As used herein, "functional fragment" refers to a fragment of a peptide, (e.g., a polypeptide), or protein that retains the ability to induce an immune response.

[0151] As used herein, the term "identity" refers to the overall monomer conservation between polymeric molecules, e.g., between polynucleotide molecules (e.g., DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of the percent identity of two polynucleotide sequences, for example, can be performed by aligning the two sequences for optimal comparison purposes (e.g., gaps can be introduced in one or both of a first and a second nucleic acid sequence for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In certain aspects, the length of a sequence aligned for comparison purposes is at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about

96% at least about 97%, at least about 98%, at least about 99% or at least about 100% of the length of the reference sequence. The nucleotides at corresponding nucleotide positions are then compared. When a position in the first sequence is occupied by the same nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which needs to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. When comparing DNA and RNA, thymine (T) and uracil (U) can be considered equivalent.

[0152] Suitable software programs are available from various sources and for alignment of both protein and nucleotide sequences. One suitable program to determine percent sequence identity is bl2seq, part of the BLAST suite of programs available from the U.S. government's National Center for Biotechnology Information BLAST website (blast.ncbi.nlm.nih.gov). Bl2seq performs a comparison between two sequences using either the BLASTN or BLASTP algorithm. BLASTN is used to compare nucleic acid sequences, while BLASTP is used to compare amino acid sequences. Other suitable programs are, e.g., Needle, Stretcher, Water, or Matcher, part of the EMBOSS suite of bioinformatics programs and also available from the European Bioinformatics Institute (EBI).

[0153] Sequence alignments can be conducted using methods such as, but not limited to, MAFFT, Clustal (ClustalW, Clustal X or Clustal Omega), or MUSCLE.

[0154] Different regions within a single polynucleotide or polypeptide target sequence that aligns with a polynucleotide or polypeptide reference sequence can each have their own percent sequence identity.

[0155] As used herein, the term "isolated" refers to a substance or entity that has been separated from at least some of the components with which it was associated (whether in nature or in an experimental setting). Isolated substances (e.g., nucleotide sequence or protein sequence) can have varying levels of purity in reference to the substances from which they have been associated. Isolated substances and/or entities can be separated from at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or more

of the other components with which they were initially associated. In some aspects, isolated agents are more than about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% pure. As used herein, a substance is "pure" if it is substantially free of other components. The term "substantially isolated" means that the compound is substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in the compound of the present disclosure. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compound of the present disclosure, or salt thereof.

[0156] A polynucleotide, vector, polypeptide, cell, or any composition disclosed herein which is "isolated" is a polynucleotide, vector, polypeptide, cell, or composition which is in a form not found in nature. Isolated polynucleotides, vectors, polypeptides, or compositions include those that have been purified to the degree that they are no longer in a form in which they are found in nature. In some aspects, a polynucleotide, vector, polypeptide, or composition that is isolated is substantially pure.

[0157] The terms "polypeptide," "peptide," and "protein" are used interchangeably herein to refer to polymers of amino acids of any length. The polymer can comprise modified amino acids. The terms also encompass an amino acid polymer that has been modified naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component. Also included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids such as homocysteine, ornithine, p-acetylphenylalanine, D-amino acids, and creatine). The term, as used herein, refers to proteins, polypeptides, and peptides of any size, structure, or function. Polypeptides include gene products, naturally occurring polypeptides, synthetic polypeptides, homologs, orthologs, paralogs, fragments and other equivalents, variants, and analogs of the foregoing. A polypeptide can be a single polypeptide or can be a multi-molecular complex such as a dimer, trimer, or tetramer. They can also comprise single chain or multichain polypeptides. Most commonly, disulfide linkages are found in multichain polypeptides. The term polypeptide can also apply to amino acid polymers in which one or more amino acid residues are an artificial

chemical analogue of a corresponding naturally occurring amino acid. In some aspects, a "peptide" can be less than or equal to about 50 amino acids long, e.g., about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acids long.

[0158] Multi-Specific Binding Protein

[0159] In some embodiments, the present disclosure provides a multi-specific binding protein that comprises a first domain (e.g., a first antigen-binding site) that binds CD19 (e.g., human CD19); a second domain (e.g., a second antigen-binding site) that binds CD3 (e.g., rodent, dog, human and/or non-human primate CD3), such as CD3ε (epsilon), CD3δ (delta), and/or CD3γ (gamma); and optionally a half-life extension domain. The multi-specific binding protein is configured to bring CD19-expressing cells, such as B cells, into spatial proximity with CD3-expressing cells, such as T cells, to enhance the cytotoxicity of the CD3-expressing cells against the CD19-expressing cells. The optional half-life extension domain can be a third domain (e.g., a third antigen-binding site) that binds serum albumin (e.g., HSA).

[0160] Each of the antigen-binding sites of the multi-specific binding protein can take various forms, such as single-chain variable fragment (scFv), Fab fragment, or single domain antibody (sdAb). In some embodiments, the first antigen-binding site comprises an scFv. In some embodiments, the second antigen-binding site comprises an scFv. In some embodiments, the third antigen-binding site comprises an sdAb.

[0161] In some embodiments, the multi-specific binding protein further comprises an antibody Fc region. The presence of an Fc region may increase the serum half-life of the multi-specific binding protein. Depending on the specific Fc subtype and variant used, the Fc region may also alter the activity (e.g., cytotoxic activity) of the multi-specific binding protein.

[0162] In some embodiments, the multi-specific binding protein does not comprise an antibody Fc region. The absence of Fc contributes to a smaller size of the multi-specific binding protein, which can exhibit improved tissue penetration and pharmacokinetic properties. In some embodiments, the multi-specific binding proteins consist of or consist essentially of the first, second, and third antigen-binding sites and the linkers between them. In some embodiments, the multi-specific binding proteins consist essentially of the first, second, and third antigen-binding sites.

[0163] In some embodiments, the multi-specific binding protein binds CD19, CD3, and/or serum albumin monovalently. The exclusion of additional binding domains reduces the risk of non-specific immune cell activation and decreases the size of the multi-specific binding protein.

[0164] ***Antigen-Binding Site That Binds CD19***

[0165] The present disclosure provides, in some embodiments, an antigen-binding site that binds CD19 (e.g., human CD19). The present disclosure also provides an antibody comprising the antigen-binding site. The CDR sequences are identified under the Kabat numbering scheme unless indicated by an asterisk (*).

[0166] **Table 1. CD19 Antibody Sequences**

Antibody	VH and HCDRs	VL and LCDRs
CNG-CD19-701	QVQLQESGPGLVKPSQTLSLTCTVS GGSISTSTMGVGWIRQHPGKGLEWI GFIWWDDDKRYNPNLKSRVTMSV DTSKNQFSLKLSSVTAADTAVYYC ARMELWSYYFDYWGQGTLVTVSS (SEQ ID NO: 1) HCDR1*: GSISTSTMGVG (SEQ ID NO: 3) HCDR1: TSTMGVG (SEQ ID NO: 4) HCDR2: FIWWDDDKRYNPNLKS (SEQ ID NO: 5) HCDR3*: ARMELWSYYFDY (SEQ ID NO: 6) HCDR3: MELWSYYFDY (SEQ ID NO: 7)	EIVLTQSPATLSLSPGERATLS CSASSSVGYMHWYQQKPGQ APRLLIYDTSKLASGIPARFSG SGSGTDFTLTISSLEPEDFAVY YCFQGSVYPFTFGQGTKLEIK (SEQ ID NO: 2) LCDR1: SASSSVGYMH (SEQ ID NO: 8) LCDR2: DTSKLAS (SEQ ID NO: 9) LCDR3: FQGSVYPFT (SEQ ID NO: 10)
	scFv: EIVLTQSPATLSLSPGERATLSCSASSSVGYMHWYQQKPGQAPRLLIY DTSKLASGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCFQGSVYPFTFG QGTKLEIKGGGGSGGGGSGGGGSQVQLQESGPGLVKPSQTLSLTCTVS GGSISTSTMGVGWIRQHPGKGLEWIGFIWWDDDKRYNPNLKSRVTMS VDTSKNQFSLKLSSVTAADTAVYYCARMELWSYYFDYWGQGTLVTV SS (SEQ ID NO: 11)	

[0167] In some embodiments, the antigen-binding site that binds CD19 is in the form of an scFv. In certain embodiments, the VH is positioned C-terminal to the VL. In some

embodiments, the VH is positioned N-terminal to the VL. In some embodiments, the VH and the VL are linked by a peptide linker, for example, a linker disclosed in subsection E below titled "Linkers." To stabilize the scFv, the amino acid residues at position 44 of the VH and at position 100 of the VL (under Kabat numbering) can be substituted by Cys, thereby facilitating the formation of a disulfide bond between the VH and the VL. Accordingly, in some embodiments, the VH and VL comprise Cys at positions 100 and 44, respectively.

[0168] [23] In some embodiments, the antigen-binding site that binds CD19 of the present disclosure comprises a VH that comprises an amino acid sequence at least 60% (e.g., at least 70%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%) identical to the VH of an antibody disclosed in Table 1, and a VL that comprises an amino acid sequence at least 60% (e.g., at least 70%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%) identical to the VL of the same antibody disclosed in Table 1. In some embodiments, the antigen-binding site comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, determined under Kabat (see Kabat et al., (1991) Sequences of Proteins of Immunological Interest, NIH Publication No. 91-3242, Bethesda), Chothia (see, e.g., Chothia C & Lesk A M, (1987), J Mol Biol 196: 901-917), MacCallum (see MacCallum R M et al., (1996) J Mol Biol 262: 732-745), IMGT (see Lefranc, (1999) The Immunologist, 7, 132-136), or any other CDR determination method known in the art, of the VH and VL sequences of an antibody disclosed in Table 1.

[0169] In some embodiments, the antigen-binding site that binds CD19 is derived from CNG-CD19-701. In some embodiments, the antigen-binding site comprises a VH comprising HCDR1, HCDR2, and HCDR3 sequences set forth in SEQ ID NOs: 3, 5, and 6, respectively, and a VL comprising LCDR1, LCDR2, and LCDR3 sequences set forth in SEQ ID NOs: 8, 9, and 10, respectively. In some embodiments, the antigen-binding site comprises a VH comprising HCDR1, HCDR2, and HCDR3 sequences set forth in SEQ ID NOs: 4, 5, and 7, respectively, and a VL comprising LCDR1, LCDR2, and LCDR3 sequences set forth in SEQ ID NOs: 8, 9, and 10, respectively. In some embodiments, the antigen-binding site comprises a VH comprising an amino acid sequence at least 60% (e.g., at least 70%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at

least 98%, at least 99%, or 100%) identical to SEQ ID NO: 1, and a VL that comprising an amino acid sequence at least 60% (e.g., at least 70%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%) identical to SEQ ID NO: 2. In some embodiments, the VH and the VL comprise the amino acid sequences of SEQ ID NOs: 1 and 2, respectively.

[0170] In some embodiments, the antigen-binding site binds human CD19 or an extracellular fragment thereof with a KD lower than or equal to 2 nM, 1 nM, or 0.5 nM, as measured by surface plasmon resonance (SPR) when the antigen-binding site is present as a monomer. In some embodiments, the antigen-binding site binds human CD19 or an extracellular fragment thereof with a KD in the range of 0.5-2 nM, in the range of 0.5-1 nM, or in the range of 0.5-0.5 nM, as measured by SPR when the antigen-binding site is present as a monomer.

[0171] In some embodiments, the antigen-binding site derived from CNG-CD19-701 binds human CD19 or an extracellular fragment thereof with a KD lower than or equal to 2 nM, 1 nM, or 0.5 nM, as measured by surface plasmon resonance (SPR) when the antigen-binding site is present as a monomer. In some embodiments, the antigen-binding site derived from CNG-CD19-701 binds human CD19 or an extracellular fragment thereof with a KD in the range of 0.5-2 nM, in the range of 0.5-1 nM, or in the range of 0.5-0.5 nM, as measured by SPR when the antigen-binding site is present as a monomer.

[0172] In some embodiments, the antigen-binding site derived from CNG-CD19-701 binds human CD19 or an extracellular fragment thereof with a KD lower than or equal to 0.4 nM, 0.3 nM, 0.2 nM, or 0.1 nM, as measured by SPR when the antigen-binding site is present as a monomer. In some embodiments, the antigen-binding site derived from CNG-CD19-701 binds human CD19 or an extracellular fragment thereof with a KD in the range of 0.5-0.4 nM, 0.5-0.3 nM, 0.5-0.2 nM, or 0.5-0.1 nM, as measured by SPR when the antigen-binding site is present as a monomer.

[0173] In some embodiments, the antigen-binding site derived from CNG-CD19-701 binds cynomolgus CD19 with a KD lower than or equal to 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, or 3 nM, as measured by SPR when the antigen-binding site is present as a monomer. In some embodiments, the antigen-binding site derived from CNG-CD19-701 binds cynomolgus CD19 with a KD in the range of 1-8 nM, 1-7 nM, 1-6 nM, 1-5 nM, 1-4 nM, or 1-3 nM, as measured by SPR when the antigen-binding site is present as a monomer.

[0174] The present disclosure also provides an antigen-binding site that competes for binding CD19 (e.g., human CD19) with an antibody or antigen-binding site comprising the VH, VL and/or scFv sequences provided in Table 1.

[0175] ***Antigen-Binding Site That Binds CD3***

[0176] The second antigen-binding site of the multi-specific binding protein binds CD3 (e.g., human CD3 and/or Macaca CD3). In some embodiments, the second antigen-binding site binds CD3ε (epsilon). In some embodiments, the second antigen-binding site binds CD3δ (delta). In some embodiments, the second antigen-binding site binds CD3γ (gamma).

[0177] In some embodiments, the second antigen-binding site of the multi-specific binding protein binds an epitope at the N-terminus of CD3ε chain. In some embodiments, the second antigen-binding site binds an epitope localized in amino acid residues 1-27 of human CD3ε extracellular domain. This epitope or a homologous variant thereof is also present in certain non-human primates. Accordingly, in certain embodiments, the second antigen-binding site binds CD3 in different primates, for example, human, new world primates (such as Callithrix jacchus, Saguinus Oedipus, or Saimiri sciureus), old world primates (such as baboons and macaques), gibbons, and non-human hominidae. Callithrix jacchus and Saguinus oedipus are new world primates belonging to the family of Callitrichidae, while Saimiri sciureus is a new world primate belonging to the family of Cebidae. In some embodiments, the second antigen-binding site binds human CD3ε and/or Macaca CD3ε. In some embodiments, the second antigen-binding site further binds Callithrix jacchus, Saguinus Oedipus, and/or Saimiri sciureus CD3ε.

[0178] **Table 2. CD3 Antibody Sequences**

Antibody	VH and HCDRs	VL and LCDRs
CNG-CD3-1	QVQLVQSGAEVKKPGASVKVSCK ASGFNIKDYYMHWVRQAPGQRLE WMGWIDLENANTIYDAKFQGRVT ITRDTSASTAYMELSSLRSEDTAV YYCARDAYGRYFYDVWGQGTLV TVSS (SEQ ID NO: 12) HCDR1*: FNIKDYYMH (SEQ ID NO: 14) HCDR1: DYYMH (SEQ ID NO: 15)	DIVMTQSPDSLAVSLGERATIN CKSSQSLLNARTGKNYLAWYQ QKPGQPPKLLIYWASTRESGVP DRFSGSGSGTDFTLTISSLQAED VAVYYCKQSYSRRTFGGGTKV EIK (SEQ ID NO: 13) LCDR1: KSSQSLLNARTGKNYLA (SEQ ID NO: 19)

Antibody	VH and HCDRs	VL and LCDRs
	HCDR2: WIDLENANTIYDAKFQG (SEQ ID NO: 16) HCDR3*: ARDAYGRYFYDV (SEQ ID NO: 17) HCDR3: DAYGRYFYDV (SEQ ID NO: 18)	LCDR2: WASTRES (SEQ ID NO: 20) LCDR3: KQSYSRRT (SEQ ID NO: 21)
	scFv: DIVMTQSPDSLAVSLGERATINCKSSQSLLNARTGKNYLAWYQQKPGQ PPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCKQS YSRRTFGGGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVK KPGASVKVSCKASGFNIKDYYMHWVRQAPGQRLEWMGWIDLENANT IYDAKFQGRVTITRDTSASTAYMELSSLRSEDTAVYYCARDAYGRYFY DVWGQGTLVTVSS (SEQ ID NO: 22) scFv with Cys substitutions: DIVMTQSPDSLAVSLGERATINCKSSQSLLNARTGKNYLAWYQQKPGQ PPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCKQS YSRRTFGCGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVK KPGASVKVSCKASGFNIKDYYMHWVRQAPGQCLEWMGWIDLENANT IYDAKFQGRVTITRDTSASTAYMELSSLRSEDTAVYYCARDAYGRYFY DVWGQGTLVTVSS (SEQ ID NO: 23)	

[0179] Where the VL and LCDR sequences are noted as "N/A," the antigen-binding site is an sdAb having a VH (e.g., VHH) only.

[0180] In some embodiments, the second antigen-binding site comprises a VH that comprises an amino acid sequence at least 60% (e.g., at least 70%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%) identical to the VH of an antibody disclosed in Table 2, and a VL that comprises an amino acid sequence at least 60% (e.g., at least 70%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%) identical to the VL of the same antibody disclosed in Table 2. In some embodiments, the antigen-binding site comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, determined under Kabat (see Kabat et al., (1991) Sequences of Proteins of Immunological Interest, NIH Publication No. 91-3242, Bethesda), Chothia (see, e.g., Chothia C & Lesk A M, (1987), J Mol Biol 196: 901-917), MacCallum (see MacCallum R M et al., (1996) J Mol Biol 262: 732-745), IMGT (see Lefranc,

(1999) The Immunologist, 7, 132-136), or any other CDR determination method known in the art, of the VH and/or VL sequences of an antibody disclosed in Table 2. In some embodiments, the antigen-binding site comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 sequences of an antibody disclosed in Table 2. In some embodiments, the antigen-binding site comprises the VH and VL sequences of an antibody disclosed in Table 2.

[0181] In some embodiments, the second antigen-binding site that binds CD3 is derived from CNG-CD3-1. In some embodiments, the second antigen-binding site comprises a VH comprising HCDR1, HCDR2, and HCDR3 sequences set forth in SEQ ID NOs: 14, 16, and 17, respectively, and a VL comprising LCDR1, LCDR2, and LCDR3 sequences set forth in SEQ ID NOs: 19, 20, and 21, respectively. In some embodiments, the second antigen-binding site comprises a VH comprising HCDR1, HCDR2, and HCDR3 sequences set forth in SEQ ID NOs: 15, 16, and 18, respectively, and a VL comprising LCDR1, LCDR2, and LCDR3 sequences set forth in SEQ ID NOs: 19, 20, and 21, respectively. In some embodiments, the second antigen-binding site comprises a VH comprising an amino acid sequence at least 60% (e.g., at least 70%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%) identical to SEQ ID NO: 12, and a VL that comprising an amino acid sequence at least 60% (e.g., at least 70%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%) identical to SEQ ID NO: 13. In some embodiments, the VH and the VL of the second antigen-binding site comprise the amino acid sequences of SEQ ID NOs: 12 and 13, respectively.

[0182] Such antigen-binding site may take the form of scFv. In certain embodiments, the VH is positioned C-terminal to the VL. In some embodiments, the VH is positioned N-terminal to the VL. In some embodiments, the VH and the VL are linked by a peptide linker, for example, a linker disclosed in subsection E below titled "Linkers." In some embodiments, the second antigen-binding site comprises the amino acid sequence of SEQ ID NO: 22. To stabilize the scFv, the amino acid residues at position 44 of the VH and at position 100 of the VL (under Kabat numbering) can be substituted by Cys, thereby facilitating the formation of a disulfide bond between the VH and the VL. Accordingly, in some embodiments, the VH and VL comprise Cys at positions 100 and 44, respectively.

[0183] In some embodiments, the second antigen-binding site comprises an sdAb comprising a VH comprising complementarity determining regions HCDR1, HCDR2, and HCDR3. In some embodiments, the VH comprises an amino acid sequence at least 60% (e.g., at least 70%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) identical to the VH of an sdAb antibody provided in Table 2. In some embodiments, the VH comprises the HCDR1, HCDR2, and HCDR3 sequences of the antibody provided in Table 2. In some embodiments, the VH comprises the amino acid sequence of the VH of an sdAb provided in Table 2.

[0184] In some embodiments, the second antigen-binding site competes for binding CD3 (e.g., human CD3 and/or Macaca CD3) with an antibody or antigen-binding fragment thereof comprising the VH, VL and/or scFv sequences provided in Table 2.

[0185] In some embodiments, the second antigen-binding site of the multi-specific binding protein binds CD3 (e.g., human CD3 and/or Macaca CD3) with a dissociation constant (KD) of about 0.1 nM – about 1 μM. The KD can be measured by a method known in the art. In some embodiments, the KD is measured by SPR to CD3 or an extracellular fragment thereof immobilized on a chip. In some embodiments, the KD is measured by flow cytometry to CD3 expressed on the surface of cells.

[0186] In some embodiments, the second antigen-binding site binds CD3 with a KD, as measured by SPR, lower than or equal to 20 nM, 15 nM, 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, 0.9 nM, 0.8 nM, 0.7 nM, 0.6 nM, 0.5 nM, 0.4 nM, 0.3 nM, 0.2 nM, 0.1 nM, 90 pM, 80 pM, 70 pM, 60 pM, 50 pM, 40 pM, 30 pM, 20 pM, or 10 pM. For example, in certain embodiments, the first antigen-binding site binds CD3 with a KD, as measured by SPR, within the range of about 10 pM – about 1 nM, about 10 pM – about 0.9 nM, about 10 pM – about 0.8 nM, about 10 pM – about 0.7 nM, about 10 pM – about 0.6 nM, about 10 pM – about 0.5 nM, about 10 pM – about 0.4 nM, about 10 pM – about 0.3 nM, about 10 pM – about 0.2 nM, about 10 pM – about 0.1 nM, about 10 pM – about 50 pM, 0.1 nM – about 10 nM, about 0.1 nM – about 9 nM, about 0.1 nM – about 8 nM, about 0.1 nM – about 7 nM, about 0.1 nM – about 6 nM, about 0.1 nM – about 5 nM, about 0.1 nM – about 4 nM, about 0.1 nM – about 3 nM, about 0.1 nM – about 2 nM, about 0.1 nM – about 1 nM, about 0.1 nM – about 0.5 nM, about 0.5 nM – about 10 nM, about 0.5 nM – about 9 nM, about 0.5 nM – about 8 nM, about 0.5 nM – about 7 nM, about

0.5 nM – about 6 nM, about 0.5 nM – about 5 nM, about 0.5 nM – about 4 nM, about 0.5 nM – about 3 nM, about 0.5 nM – about 2 nM, about 0.5 nM – about 1 nM, about 1 nM – about 10 nM, about 1 nM – about 9 nM, about 1 nM – about 8 nM, about 1 nM – about 7 nM, about 1 nM – about 6 nM, about 1 nM – about 5 nM, about 1 nM – about 4 nM, about 1 nM – about 3 nM, about 1 nM – about 2 nM, about 2 nM – about 10 nM, about 3 nM – about 10 nM, about 4 nM – about 10 nM, about 5 nM – about 10 nM, about 6 nM – about 10 nM, about 7 nM – about 10 nM, about 8 nM – about 10 nM, or about 9 nM – about 10 nM.

[0187] In some embodiments, the second antigen-binding site binds CD3 with a KD, as measured by BLI, lower than or equal to 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, 0.9 nM, 0.8 nM, 0.7 nM, 0.6 nM, 0.5 nM, 0.4 nM, 0.3 nM, 0.2 nM, or 0.1 nM. For example, in certain embodiments, the first antigen-binding site binds CD3 with a KD, as measured by BLI, within the range of about 0.1 nM – about 20 nM, about 0.1 nM – about 19 nM, about 0.1 nM – about 18 nM, about 0.1 nM – about 17 nM, about 0.1 nM – about 16 nM, about 0.1 nM – about 15 nM, about 0.1 nM – about 14 nM, about 0.1 nM – about 13 nM, about 0.1 nM – about 12 nM, about 0.1 nM – about 11 nM, 0.1 nM – about 10 nM, about 0.1 nM – about 9 nM, about 0.1 nM – about 8 nM, about 0.1 nM – about 7 nM, about 0.1 nM – about 6 nM, about 0.1 nM – about 5 nM, about 0.1 nM – about 4 nM, about 0.1 nM – about 3 nM, about 0.1 nM – about 2 nM, about 0.1 nM – about 1 nM, about 0.1 nM – about 0.5 nM, about 1 nM – about 50 nM, about 1 nM – about 40 nM, about 1 nM – about 30 nM, about 1 nM – about 20 nM, about 1 nM – about 19 nM, about 1 nM – about 18 nM, about 1 nM – about 17 nM, about 1 nM – about 16 nM, about 1 nM – about 15 nM, about 1 nM – about 14 nM, about 1 nM – about 13 nM, about 1 nM – about 12 nM, about 1 nM – about 11 nM, about 1 nM – about 10 nM, or about 1 nM – about 5 nM.

[0188] In some embodiments, the second antigen-binding site binds CD3 (e.g., human CD3, e.g., human CD3ε) with a KD, as measured by SPR, greater than or equal to 1 nM, 2 nM, 3 nM, 4 nM, 5 nM, 6 nM, 7 nM, 8 nM, 9 nM, 10 nM, 20 nM, 30 nM, 40 nM, 50 nM, 60 nM, 70 nM, 80 nM, 90 nM, or 100 nM. In some embodiments, the second antigen-binding site binds CD3 with a KD, as measured by SPR, within the range of about 1 nM – about 100 nM, about 1 nM – about 90 nM, about 1 nM – about 80 nM, about 1 nM – about 70 nM, about 1 nM – about 60 nM, about 1 nM – about 50 nM, about 1 nM – about 40 nM, about 1 nM – about 30 nM, about 1 nM – about 20 nM, about 1 nM – about 10 nM, about 10 nM – about 100 nM, about 10 nM – about

90 nM, about 10 nM – about 80 nM, about 10 nM – about 70 nM, about 10 nM – about 60 nM, about 10 nM – about 50 nM, about 10 nM – about 40 nM, about 10 nM – about 30 nM, or about 10 nM – about 20 nM. In some embodiments, the second antigen-binding site binds CD3 (e.g., human CD3, e.g., human CD3ε) with a KD, as measured by BLI, greater than or equal to 10 nM, 20 nM, 30 nM, 40 nM, 50 nM, 60 nM, 70 nM, 80 nM, 90 nM, 100 nM, 200 nM, 300 nM, 400 nM, 500 nM, 600 nM, 700 nM, 800 nM, 900 nM, or 1 μM. In some embodiments, the second antigen-binding site binds CD3 with a KD, as measured by BLI, within the range of about 10 nM – about 1 μM, about 10 nM – about 900 nM, about 10 nM – about 800 nM, about 10 nM – about 700 nM, about 10 nM – about 600 nM, about 10 nM – about 500 nM, about 10 nM – about 400 nM, about 10 nM – about 300 nM, about 10 nM – about 200 nM, about 10 nM – about 100 nM, about 100 nM – about 1 μM, about 100 nM – about 900 nM, about 100 nM – about 800 nM, about 100 nM – about 700 nM, about 100 nM – about 600 nM, about 100 nM – about 500 nM, about 100 nM – about 400 nM, about 100 nM – about 300 nM, or about 100 nM – about 200 nM.

[0189] In some embodiments, the second antigen-binding site, when present in the form of an Fab, has a melting temperature of at least 60 °C, at least 65 °C, at least 70 °C, at least 75 °C, or at least 80 °C. In some embodiments, the second antigen-binding site, when present in the form of an Fab, has a melting temperature in the range of 60-85 °C, 60-80 °C, 60-75 °C, 60-70 °C, 60-65 °C, 65-85 °C, 65-80 °C, 65-75 °C, 65-70 °C, 70-85 °C, 70-80 °C, 70-75 °C, 75-85 °C, 75-80 °C, or 80-85 °C.

[0190] ***Half-life Extension Domain***

[0191] In some embodiments, the second antigen-binding site, when present in the form of an Fab, has a melting temperature of at least 60 °C, at least 65 °C, at least 70 °C, at least 75 °C, or at least 80 °C. In some embodiments, the second antigen-binding site, when present in the form of an Fab, has a melting temperature in the range of 60-85 °C, 60-80 °C, 60-75 °C, 60-70 °C, 60-65 °C, 65-85 °C, 65-80 °C, 65-75 °C, 65-70 °C, 70-85 °C, 70-80 °C, 70-75 °C, 75-85 °C, 75-80 °C, or 80-85 °C.

[0192] In some embodiments, the multi-specific binding protein comprises a half-life extension domain. As used herein, the term "half-life extension domain" refers to a protein domain that prolongs the half-life of a protein to which it is fused, within a subject (e.g., the blood of the subject). Exemplary half-life extension domains include Fc domains, serum albumin domains, and protein domains that bind serum albumin. In some embodiments, the half-life

extension domain in the multi-specific binding protein comprises a third antigen-binding site that binds serum albumin (e.g., HSA). It is contemplated that a serum albumin binding domain may facilitate recycling of the multi-specific binding protein through binding to neonatal Fc receptor (FcRn), thereby extending the serum half-life of the multi-specific binding protein. Accordingly, in certain embodiments, the third antigen-binding site does not bind the D-III domain of HSA (the domain that mediates the interaction between HSA and FcRn). In some embodiments, the third antigen-binding site extends the serum half-life of the multi-specific binding protein.

[0193] In some embodiments, the third antigen-binding site is an antigen-binding site that binds serum albumin (e.g., human serum albumin (HSA)) derived from the single domain antibodies listed in Table 3. The CDR sequences are identified under the Kabat numbering scheme unless indicated by an asterisk (*).

i.Table 3. Serum Albumin Antibody Sequences

Antibody	VH and HCDRs
CNG-HSA-101	KVQLVESGGGLVQPGGSLRLSCAASGFTFSSFGMTWVRQAPGKGLEWVSSISGSGSDTLYADSVRGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTIGGSLSPSSQGTLVTVSS (SEQ ID NO: 24) HCDR1*: FTFSSFGMT (SEQ ID NO: 25) HCDR1: SFGMT (SEQ ID NO: 26) HCDR2: SISGSGSDTLYADSVRG (SEQ ID NO: 27) HCDR3*: TIGGSLSP (SEQ ID NO: 28) HCDR3: GGSLSP (SEQ ID NO: 29)

[0194] In some embodiments, the antigen-binding site that binds serum albumin comprises a VH that comprises an amino acid sequence at least 60% (e.g., at least 70%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%) identical to the VH of an antibody disclosed in Table 3. In some embodiments, the antigen-binding site comprises the HCDR1, HCDR2, and HCDR3, determined under Kabat (see Kabat et al., (1991) Sequences of Proteins of Immunological Interest, NIH Publication No. 91-3242, Bethesda), Chothia (see, e.g., Chothia C & Lesk A M, (1987), J Mol Biol 196: 901-917), MacCallum (see MacCallum R M et al., (1996)

J Mol Biol 262: 732-745), IMGT (see Lefranc, (1999) The Immunologist, 7, 132-136), or any other CDR determination method known in the art, of the VH sequence of an antibody disclosed in Table 3. In some embodiments, the antigen-binding site comprises the HCDR1, HCDR2, and HCDR3 sequences of an antibody disclosed in Table 3. In some embodiments, the antigen-binding site comprises the VH sequence of an antibody disclosed in Table 3.

[0195] In some embodiments, the antigen-binding site that binds serum albumin is derived from CNG-HSA-101. In some embodiments, the antigen-binding site comprises a VH comprising HCDR1, HCDR2, and HCDR3 sequences set forth in SEQ ID NOs: 25, 27, and 28, respectively. In some embodiments, the antigen-binding site comprises a VH comprising HCDR1, HCDR2, and HCDR3 sequences set forth in SEQ ID NOs: 26, 27, and 29, respectively. In some embodiments, the antigen-binding site comprises a VH comprising an amino acid sequence at least 60% (e.g., at least 70%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%) identical to SEQ ID NO: 24. In some embodiments, the VH comprises the amino acid sequence of SEQ ID NO: 24.

[0196] In some embodiments, the antigen-binding site binds human serum albumin with a KD lower than or equal to 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, or 3 nM, as measured by SPR when the antigen-binding site is present as a monomer. In some embodiments, the antigen-binding site binds human serum albumin with a KD in the range of 1-10 nM, 1-9 nM, 1-8 nM, 1-7 nM, 1-6 nM, 1-5 nM, 1-4 nM, or 1-3 nM, as measured by SPR when the antigen-binding site is present as a monomer.

[0197] In some embodiments, the antigen-binding site derived from CNG-HSA-101 binds cynomolgus serum albumin with a KD lower than or equal to 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, or 3 nM, as measured by SPR when the antigen-binding site is present as a monomer. In some embodiments, the antigen-binding site derived from CNG-HSA-101 binds cynomolgus serum albumin with a KD in the range of 1-9 nM, 1-8 nM, 1-7 nM, 1-6 nM, 1-5 nM, 1-4 nM, or 1-3 nM, as measured by SPR when the antigen-binding site is present as a monomer.

[0198] In some embodiments, the antigen-binding site derived from CNG-HSA-101 binds mouse serum albumin with a KD lower than or equal to 100 nM, 90 nM, 80 nM, 70 nM, 60 nM, 50 nM, 40 nM, 30 nM, 20 nM, or 10 nM, as measured by SPR when the antigen-binding site is present as a monomer. In some embodiments, the antigen-binding site derived from CNG-HSA-

101 binds mouse serum albumin with a KD in the range of 1-100 nM, 1-90 nM, 1-80 nM, 1-70 nM, 1-60 nM, 1-50 nM, 1-40 nM, 1-30 nM, 1-20 nM, or 1-10 nM, as measured by SPR when the antigen-binding site is present as a monomer.

[0199] In some embodiments, the antigen-binding site derived from CNG-HSA-101 binds human serum albumin with a first KD and binds mouse serum albumin with a second KD, wherein the ratio of the second KD to the first KD is in the range of 0.5-10, 0.5-9, 0.5-8, 0.5-7, 0.5-6, 0.5-5, 0.5-4, 0.5-3, 0.5-2, 0.9-10, 0.9-9, 0.9-8, 0.9-7, 0.9-6, 0.9-5, 0.9-4, 0.9-3, 0.9-2, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2. It is understood that an antigen-binding site having a ratio closer to 1 has a more similar affinity to mouse serum albumin relative to affinity to human serum albumin, which allows assessment of the pharmacokinetics of the antigen-binding site or a protein comprising the same using a mouse model at higher accuracy.

[0200] Melting temperature represents the thermostability of the antigen-binding site and can be measured by differential scanning fluorimetry, for example, as described in Durowoju et al. (2017) J. Vis. Exp. (121): 55262. The thermostability of an antibody or fragment thereof may be enhanced by grafting CDRs onto stable frameworks, introducing non-canonical disulfide bonds, and other mutagenesis, as described in McConnell et al. (2014) MAbs, 6(5): 1274-82; and Goldman et al. (2017) Front. Immunol., 8: 865. In some embodiments, the antigen-binding site derived from CNG-HSA-101 has a melting temperature greater than or equal to 60 °C, as measured by differential scanning fluorimetry. In some embodiments, the antigen-binding site derived from CNG-HSA-101 has a melting temperature greater than or equal to 65 °C, as measured by differential scanning fluorimetry.

[0201] In some embodiments, the third antigen-binding site competes for binding serum (e.g., human serum albumin) and/or competes for binding protein A with an antibody or antigen-binding site comprising the VH sequence provided in Table 3.

[0202] In some embodiments, the third antigen-binding site has a melting temperature of at least 50 °C, at least 55 °C, at least 56 °C, at least 57 °C, at least 58 °C, at least 59 °C, at least 60 °C, at least 61 °C, at least 62 °C, at least 63 °C, at least 64 °C, at least 65 °C, at least 70 °C, at least 75 °C, or at least 80 °C. In some embodiments, the third antigen-binding site has a melting temperature in the range of 50-80 °C, 50-70 °C, 50-65 °C, 50-60 °C, 50-55 °C, 55-70 °C, 55-65 °C, 55-60 °C, 56-65 °C, 56-60 °C, 57-65 °C, 57-60 °C, 58-65 °C, 58-60 °C, 59-65 °C, 59-60 °C, 60-80 °C, 60-75 °C, 60-70 °C, 60-65 °C, 65-80 °C, 65-75 °C, 65-70 °C, 70-80 °C, or 70-75 °C.

[0203] ***Construct Formats***

[0204] The first, second, and third antigen-binding sites may take various forms. In some embodiments, the first, second, and/or third antigen-binding sites comprises two antibody variable domains (e.g., a VH and a VL). The VH and the VL can be mutated to introduce a disulfide bond (e.g., between H44 and L100) that stabilizes the antigen-binding site (see, Zhao et al. (2010) Int. J. Mol. Sci., 12(1):1-11). In some embodiments, the first, second, and/or third antigen-binding sites comprises a single antibody variable domain (e.g., an sdAb).

[0205] In an antigen-binding site that contains a VH and a VL, the VH and the VL can be linked to form an scFv. The VH can be positioned N-terminal or C-terminal to the VL. The VH and the VL are typically linked through a linker, such as a peptide linker. Exemplary sequences of peptide linkers are provided in subsection E below titled "Linkers." In some embodiments, the VH of an antigen-binding domain is connected to the VL of the antigen-binding domain through a peptide linker having an amino acid sequence listed in Table 4. In particular embodiments, the VH of an antigen-binding domain is connected to the VL of the antigen-binding domain through a peptide linker having the amino acid sequence of SEQ ID NO: 36, 37, or 40, wherein the VH is positioned N-terminal to the VL. In other particular embodiments, the VH of an antigen-binding domain is connected to the VL of the antigen-binding domain through a peptide linker having the amino acid sequence of SEQ ID NO: 36, 37, or 40, wherein the VH is positioned C-terminal to the VL.

[0206] In some embodiments, the VH and the VL are present on separate polypeptide chains, and the formation of a VH-VL complex is facilitated by additional domains, such as antibody constant regions CH1 and CL. Accordingly, in certain embodiments, the multi-specific binding protein comprises an Fab comprising a VH and a VL disclosed herein.

[0207] In some embodiments, a multi-specific binding protein of the present disclosure comprises a first antigen-binding site comprising a single antibody variable domain, a second antigen-binding site comprising a single antibody variable domain, and a third antigen-binding site comprising a single antibody variable domain. In some embodiments, the multi-specific binding protein comprises a first antigen-binding site in an sdAb format, a second antigen-binding site in an sdAb format, and a third antigen-binding site in an sdAb format.

[0208] In some embodiments, a multi-specific binding protein of the present disclosure comprises a first antigen-binding site comprising a single antibody variable domain, a second

antigen-binding site comprising a single antibody variable domain, and a third antigen-binding site comprising two antibody variable domains. In some embodiments, the multi-specific binding protein comprises a first antigen-binding site in an sdAb format, a second antigen-binding site in an sdAb format, and a third antigen-binding site in an scFv format.

[0209] In some embodiments, a multi-specific binding protein of the present disclosure comprises a first antigen-binding site comprising a single antibody variable domain, a second antigen-binding site comprising two antibody variable domains, and a third antigen-binding site comprising a single antibody variable domain. In some embodiments, the multi-specific binding protein comprises a first antigen-binding site in an sdAb format, a second antigen-binding site in an scFv format, and a third antigen-binding site in an sdAb format.

[0210] In some embodiments, a multi-specific binding protein of the present disclosure comprises a first antigen-binding site comprising a single antibody variable domain, a second antigen-binding site comprising two antibody variable domains, and a third antigen-binding site comprising two antibody variable domains. In some embodiments, the multi-specific binding protein comprises a first antigen-binding site in an sdAb format, a second antigen-binding site in an scFv format, and a third antigen-binding site in an scFv format.

[0211] In some embodiments, a multi-specific binding protein of the present disclosure comprises a first antigen-binding site comprising two antibody variable domains, a second antigen-binding site comprising a single antibody variable domain, and a third antigen-binding site comprising a single antibody variable domain. In some embodiments, the multi-specific binding protein comprises a first antigen-binding site in an scFv format, a second antigen-binding site in an sdAb format, and a third antigen-binding site in an sdAb format.

[0212] In some embodiments, a multi-specific binding protein of the present disclosure comprises a first antigen-binding site comprising two antibody variable domains, a second antigen-binding site comprising a single antibody variable domain, and a third antigen-binding site comprising two antibody variable domains. In some embodiments, the multi-specific binding protein comprises a first antigen-binding site in an scFv format, a second antigen-binding site in an sdAb format, and a third antigen-binding site in an scFv format.

[0213] In some embodiments, a multi-specific binding protein of the present disclosure comprises a first antigen-binding site comprising two antibody variable domains, a second antigen-binding site comprising two antibody variable domains, and a third antigen-binding site

comprising a single antibody variable domain. In some embodiments, the multi-specific binding protein comprises a first antigen-binding site in an scFv format, a second antigen-binding site in an scFv format, and a third antigen-binding site in an sdAb format.

[0214] In some embodiments, a multi-specific binding protein of the present disclosure comprises a first antigen-binding site comprising two antibody variable domains, a second antigen-binding site comprising two antibody variable domains, and a third antigen-binding site comprising two antibody variable domains. In some embodiments, the multi-specific binding protein comprises a first antigen-binding site in an scFv format, a second antigen-binding site in an scFv format, and a third antigen-binding site in an scFv format.

[0215] The three antigen-binding sites of the multi-specific binding protein can be linked in any one of the following orientations in an amino-to-carboxyl direction:

[0216] (i) the first antigen-binding site (CD19 binding domain) – the second antigen-binding site (CD3 binding domain) – the third antigen-binding site (serum albumin binding domain);

[0217] (ii) the first antigen-binding site (CD19 binding domain) – the third antigen-binding site (serum albumin binding domain) – the second antigen-binding site (CD3 binding domain);

[0218] (iii) the second antigen-binding site (CD3 binding domain) – the first antigen-binding site (CD19 binding domain) – the third antigen-binding site (serum albumin binding domain);

[0219] (iv) the second antigen-binding site (CD3 binding domain) – the third antigen-binding site (serum albumin binding domain) – the first antigen-binding site (CD19 binding domain);

[0220] (v) the third antigen-binding site (serum albumin binding domain) – the first antigen-binding site (CD19 binding domain) – the second antigen-binding site (CD3 binding domain); and

[0221] (vi) the third antigen-binding site (serum albumin binding domain) – the second antigen-binding site (CD3 binding domain) – the first antigen-binding site (CD19 binding domain),

[0222] wherein the dashes above represent a peptide bond and/or a linker (e.g., peptide linker).

[0223] In some embodiments, the third antigen-binding site is not positioned between the first antigen-binding site and the second antigen-binding site. It is contemplated that constructs having such formats have favorable therapeutic efficacy and in vivo half-life. In some embodiments, the third antigen-binding site is positioned N-terminal to both the first antigen-binding site and the second antigen-binding site or C-terminal to both the first antigen-binding site and the second antigen-binding site. In some embodiments, the third antigen-binding site is positioned N-terminal to both the first antigen-binding site and the second antigen-binding site. In some embodiments, the third antigen-binding site is positioned C-terminal to both the first antigen-binding site and the second antigen-binding site.

[0224] The position (N-terminal or C-terminal) of one antigen-binding site relative to another is determined under the definitions of "N-terminal" and "C-terminal" as known in the art if a single polypeptide chain comprises both antigen-binding sites. It is understood that if an antigen-binding site comprises two separate polypeptide chains, its position (N-terminal or C-terminal) relative to another antigen-binding site (either having a single polypeptide chain or two polypeptide chains) can be similarly determined if a single polypeptide chain comprises at least one polypeptide chain of the former and at least one polypeptide chain of the latter. It is further understood that if antigen-binding site A is N-terminal to antigen-binding site B and antigen-binding site B is N-terminal to antigen-binding site C, it is deemed that antigen-binding site A is positioned N-terminal to antigen-binding site C even if antigen-binding sites A and C are not present in any single, common polypeptide chain. More complex structures of multi-specific binding proteins are also contemplated, some of which may have orientations difficult to characterize using the terms of "N-terminal" and "C-terminal" as described above due to, for example, different relative positions of two antigen-binding sites on one polypeptide chain versus another polypeptide chain, or the presence of a loop structure.

[0225] According to the present disclosure, the multi-specific binding proteins and its constituent binding domains are in the form of one or more polypeptides. Such polypeptides may include proteinaceous parts and non-proteinaceous parts (e.g.,. chemical linkers or chemical cross-linking agents such as glutaraldehyde). In some embodiments, a multi-specific binding protein of the present disclosure includes a first antigen-binding site, a second antigen-binding site, and a third antigen-binding site, all of which are linked together to form a single polypeptide chain. In some embodiments, the first, second, and third antigen-binding sites take the forms of

scFv and/or sdAb, for example, in a combination as described above, to form a single polypeptide chain.

[0226] ***Linkers***

[0227] As noted above, the antigen-binding sites of the multi-specific binding proteins of the present disclosure can be linked through a peptide bond or a linker (e.g., peptide linker). In some embodiments, at least two adjacent antigen-binding sites are connected by a linker (e.g., peptide linker). In some embodiments, each of the two adjacent antigen-binding sites are connected by a linker (e.g., peptide linker).

[0228] In some embodiments, the three antigen-binding sites of the multi-specific binding protein can be linked by linkers (e.g., peptide linkers) denoted as L1 and L2 in any one of the following orientations in an amino-to-carboxyl direction:

[0229] (i) the first antigen-binding site (CD19 binding domain) – L1 – the second antigen-binding site (CD3 binding domain) – L2 – the third antigen-binding site (serum albumin binding domain);

[0230] (ii) the first antigen-binding site (CD19 binding domain) – L1 – the third antigen-binding site (serum albumin binding domain) – L2 – the second antigen-binding site (CD3 binding domain);

[0231] (iii) the second antigen-binding site (CD3 binding domain) – L1 – the first antigen-binding site (CD19 binding domain) – L2 – the third antigen-binding site (serum albumin binding domain);

[0232] (iv) the second antigen-binding site (CD3 binding domain) – L1 – the third antigen-binding site (serum albumin binding domain) – L2 – the first antigen-binding site (CD19 binding domain);

[0233] (v) the third antigen-binding site (serum albumin binding domain) – L1 – the first antigen-binding site (CD19 binding domain) – L2 – the second antigen-binding site (CD3 binding domain); and (vi) the third antigen-binding site (serum albumin binding domain) – L1 – the second antigen-binding site (CD3 binding domain) – L2 – the first antigen-binding site (CD19 binding domain). It is appreciated that in a given construct, L1, L2, or both L1 and L2 may be replaced with a peptide bond.

[0234] It is understood that if a single polypeptide chain comprises two adjacent antigen-binding sites, the peptide linker connecting the two antigen-binding sites represents the amino

acid sequence between them. If an antigen-binding site comprises two separate polypeptide chains, one of which is present in a single, common polypeptide as an adjacent antigen-binding site or a polypeptide chain thereof, the peptide linker connecting the two antigen-binding sites represents the amino acid sequence between them in the common, single polypeptide.

[0235] In some embodiments, the linkers L1 and L2 are peptide linkers. Suitable lengths of L1 and L2 can be independently selected. For example, in certain embodiments, L1 and/or L2 are about 50 or less amino acid residues in length. In some embodiments, L1 consists of about 50 or less amino acid residues. In some embodiments, L1 consists of about 20 or less amino acid residues. In some embodiments, L2 consists of about 50 or less amino acid residues. In some embodiments, L2 consists of about 20 or less amino acid residues. In some embodiments, L1 and L2 independently consist of about 50 or less amino acid residues. In some embodiments, L1 and L2 independently consist of about 20 or less amino acid residues.

[0236] In some embodiments, peptide linkers L1 and L2 have an optimized length and/or amino acid composition. In some embodiments, L1 and L2 are of the same length and have the same amino acid composition. In some embodiments, L1 and L2 are different. In some embodiments, L1 and/or L2 are "short," i.e., consist of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 amino acid residues. Thus, in certain instances, the linkers consist of about 12 or less amino acid residues. In some embodiments, L1 and/or L2 are "long," e.g., consist of 15, 20, or 25 amino acid residues. In some embodiments, L1 and/or L2 consist of about 3 to about 15, for example, 8, 9 or 10 contiguous amino acid residues.

[0237] Regarding the amino acid composition of L1 and L2, peptides are selected with properties that confer flexibility to multi-specific binding protein of the present disclosure, do not interfere with the binding domains as well as resist cleavage from proteases. For example, glycine and serine residues generally provide protease resistance. Examples of the linkers suitable for linking the domains in the multi-specific binding protein include but are not limited to (GS)n, (GGS)n, (GGGS)n, (GGSG)n, (GGSGG)n, and (GGGGS)n, wherein n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20. In some embodiments, L1 and/or L2 are independently selected from the peptide sequences listed in Table 4. In some embodiments, L1 and/or L2 are independently selected from SEQ ID NOs: 30-40. In some embodiments, L1 and/or L2 are independently selected from SEQ ID NOs: 36, 37, or 40. In some embodiments, L1 and/or L2 comprise the amino acid sequence of SEQ ID NO: 36, 37, or 40. In some embodiments, L1 and/or

L2 consist of the amino acid sequence of 36, 37, or 40. In some embodiments, L1 and L2 each comprise the amino acid sequence of SEQ ID NO: 36, 37, or 40. In some embodiments, L1 and L2 each consist of the amino acid sequence of SEQ ID NO: 36, 37, or 40.

[0238] Table 4 Sequences of Exemplary Peptide Linkers

Linker	SEQ ID NO	Length	Amino Acid Sequence
$(GS)_{10}$	30	20	GSGSGSGSGSGSGSGSGS
$(GGS)_{10}$	31	30	GGSGGSGGSGGSGGSGGSGGSGGSGGS
$(GGGS)_{10}$	32	40	GGGSGGGSGGGSGGGSGGGSGGGSGGGSGGG SGGGSGGGS
$(GGSG)_{10}$	33	40	GGSGGGSGGGSGGGSGGGSGGGSGGGSGGGS GGGSGGGSG
$(GGSGG)_{10}$	34	50	GGSGGGGSGGGGSGGGGSGGGGSGGGGSGGG GSGGGGSGGGGSGGGGSGG
$(GGGGS)_{10}$	35	50	GGGGSGGGGSGGGGSGGGGSGGGGSGGGGSG GGGSGGGGSGGGGSGGGGS
$(GGGGS)_4$	36	20	GGGGSGGGGSGGGGSGGGGS
$(GGGGS)_3$	37	15	GGGGSGGGGSGGGGS
$(GGGGS)_{20}$	38	100	GGGGSGGGGSGGGGSGGGGSGGGGSGGGGSG GGGSGGGGSGGGGSGGGGSGGGGSGGGGSGG GGSGGGGSGGGGSGGGGSGGGGSGGGGSGGG GSGGGGS
$(GGSGG)_{20}$	39	100	GGSGGGGSGGGGSGGGGSGGGGSGGGGSGGG GSGGGGSGGGGSGGGGSGGGGSGGGGSGGGG SGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS GGGGSGG
Asymmetrical linker	40	9	GGGGSGGGS

[0239] A linker, such as a peptide linker disclosed herein, can also be used to connect the VH and VL of an scFv, as mentioned in subsection D above titled "Construct Formats."

[0240] Multi-Specific Binding Proteins

[0241] Listed below in Table 5 is multi-specific binding proteins comprising an scFv that binds CD19, an scFv that binds CD3, and an sdAb that binds serum albumin.

[0242] Table 5. Multispecific Binding Proteins

Construct	Format[1]	CD19 Binder	CD3 Binder[2]	HSA Binder
tAB0050 (SEQ ID NO: 41)	HSA:CD19:CD3	CNG-CD19-701 (SEQ ID NO: 11)	CNG-CD3-1 (SEQ ID NO: 22)	CNG-HSA-101 (SEQ ID NO: 24)

[0243] [1] The multi-specific binding proteins in this table are present as a single polypeptide. The format shows the order of CD19-binding scFv, the CD3-binding scFv, and the HSA-binding sdAb, from the N-terminus to the C-terminus.
[2] The CD3-binding scFv sequences can contain or lack Cys substitutions at position 44 of VH and position 100 of VL. As a result, two sequences are provided for scFv derived from each of the antibodies CNG-CD3-1 (see also Table 2).

[0244] tAB0050 (SEQ ID NO: 41)

[0245] KVQLVESGGGLVQPGGSLRLSCAASGFTFSSFGMTWVRQAPGKGLEWVSSISGS GSDTLYADSVRGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTIGGSLSPSSQGTLVTVSSGGG GSGGGSEIVLTQSPATLSLSPGERATLSCSASSSVGYMHWYQQKPGQAPRLLIYDTSKLASGIPA RFSGSGSGTDFTLTISSLEPEDFAVYYCFQGSVYPFTFGQGTKLEIKGGGGSGGGGSGGGGSQVQ LQESGPGLVKPSQTLSLTCTVSGGSISTSTMGVGWIRQHPGKGLEWIGFIWWDDDKRYNPNLKS RVTMSVDTSKNQFSLKLSSVTAADTAVYYCARMELWSYYFDYWGQGTLVTVSSGGGGSGGG SDIVMTQSPDSLAVSLGERATINCKSSQSLLNARTGKNYLAWYQQKPGQPPKLLIYWASTRESG VPDRFSGSGSGTDFTLTISSLQAEDVAVYYCKQSYSRRTFGGGTKVEIKGGGGSGGGGSGGGGS GGGGSQVQLVQSGAEVKKPGASVKVSCKASGFNIKDYYMHWVRQAPGQRLEWMGWIDLENA NTIYDAKFQGRVTITRDTSASTAYMELSSLRSEDTAVYYCARDAYGRYFYDVWGQGTLVTVSS

[0246] The antigen-binding sites listed in a given row of Table 5 can be linked, in the orientation specified in the row, through peptide linkers described in subsection E above. In some embodiments, at least two adjacent antigen-binding sites are linked by a peptide linker having the amino acid sequence of SEQ ID NO: 40. In some embodiments, each of the two adjacent antigen-binding sites are linked by a peptide linker having the amino acid sequence of SEQ ID NO: 40, thereby forming a multi-specific binding protein present in a single polypeptide.

[0247] In some embodiments, the multi-specific binding protein comprises, from N-terminus to C-terminus, SEQ ID NOs: 24, 11, and 22. In some embodiments, the multi-specific binding protein comprises the amino acid sequence of SEQ ID NO: 41.

[0248] In some embodiments, the multi-specific binding protein comprises an antigen-binding site that binds CD19 as disclosed herein, an antigen-binding site that binds CD3, and a half-life extension domain comprising an antibody Fc region. The multi-specific binding protein can take various formats to combine the antigen-binding sites and the Fc region.

[0249] In some embodiments, the multi-specific binding protein comprises an anti-CD19 antibody in an IgG antibody format fused with a CD3-binding scFv at the C-terminus of the IgG Fc region. In some embodiments, the multi-specific binding protein comprises a first polypeptide

chain comprising, from the N-terminus to the C-terminus, the VH of an antigen-binding site that binds CD19, CH1 domain, hinge, CH2 domain, and CH3 domain of an IgG antibody (e.g., human IgG1, IgG2, IgG3, or IgG4), and an scFv that binds CD3; and a second polypeptide chain comprising, from the N-terminus to the C-terminus, the VL of the antigen-binding site that binds CD19 and light chain constant (CL) domain of the IgG antibody. In some embodiments, the scFv that binds CD3 comprises a VL domain positioned N-terminal to a VH domain. In some embodiments, the IgG antibody is a human IgG1 antibody. In some embodiments, the multi-specific binding protein comprises two of the first polypeptide chain and two of the second polypeptide chain, thereby forming a dimeric antibody Fc region.

[0250] ***Nucleic Acid Delivery Systems***

[0251] In certain embodiments, the present disclosure provides for an polynucleotide (including an isolated polynucleotide) which may encode a multi-specific binding protein according to an aspect of this disclosure. In an non-limiting example, the polynucleotide includes an messenger ribonucleic acid (mRNA), at least a portion of thereof encoding multi-specific binding protein according to an aspect of this disclosure. In another aspect of the disclosure includes a first polynucleotide with an mRNA encoding a first antigen-binding site that binds CD19, a second polynucleotide with an mRNA encoding a second antigen-binding site that binds CD3, and a third polynucleotide with an mRNA encoding a half-life extension domain.

[0252] The polynucleotide may be configured for administration directly, configured for administration in a composition including other mRNA, be encoded in one or more polynucleotides for expression in a cell, and/or may be encoded in DNA, RNA, or mRNA for administration.

[0253] In some aspects, the polynucleotide may be an expression construction. "Expression construct" refers to an engineered DNA or RNA molecule designed to drive the production of a specific protein or RNA in a host cell. It typically contains regulatory elements such as a promoter to initiate transcription, an enhancer to increase expression levels, a coding sequence for the gene of interest, and a terminator to end transcription. Additional features like selectable markers, tags for protein purification, or sequences for proper localization can also be included. In an embodiment, the expression construct is a RNA. In an alternative embodiment, the expression construct is an mRNA. In an alternative embodiment, the expression construct is an cDNA.

[0254] In some embodiments, the expression construct may have the following formula:

5'UTR—coding region—3' UTR—Poly(A).

[0255] In some embodiments, the expression construct may have the following formula:

5'UTR—signal—coding region— 3' UTR—Poly(A).

[0256] In some embodiments, the expression construct may have the following formula:

5'CAP-5'UTR—signal—coding region—3'UTR —Poly(A).

[0257] In some embodiments, the expression construct may have the following formula:

5'CAP-5'UTR—signal—coding region – localization—3' UTR—Poly(A).

[0258] where "UTRs" are the untranslated regions located at the 5' and 3' ends of an mRNA construct, and "Poly(A)" refers to the polyadenylation site of the mRNA.

[0259] Generally the term "5' UTR" refers to a part of the nucleic acid molecule which is located 5' (upstream) of the open reading frame of the mRNA. In the case of srRNA, the open reading frame encodes the viral non-structural proteins while the sequence of interest is encoded in the subgenomic fragment of the viral RNA. Thus, the 5'UTR is upstream of nsP1 open reading frame. In addition, the subgenomic RNA of the srRNA has a 5'UTR. Thus, the subgenomic RNA containing a sequence of interest encoding a protein of interest contains a 5'UTR. Typically, the 5'UTR starts with the transcriptional start site and ends with one nucleotide before the start codon of the open reading frame. The 5'UTR may comprise elements for controlling gene expression, also called regulatory elements. Such regulatory elements may be, for example, ribosomal binding sites or a 5'-Terminal Oligopyrimidine Tract. The 5'UTR may be post transcriptionally modified, for example by addition of a 5'-CAP.

[0260] As used herein "5'-CAP" (or a 5'-CAP-Structure) is typically a modified nucleotide (CAP analogue), particularly a guanine nucleotide, added to the 5' end of an mRNA molecule. In certain implementations, the 5'-CAP is added using a 5'-5'-triphosphate linkage (also named m7GpppN). In the context of the present disclosure, a 5' CAP structure may also be formed in chemical RNA synthesis or RNA in vitro transcription (co-transcriptional capping) using cap analogues, or a cap structure may be formed in vitro using capping enzymes (e.g., commercially available capping kits).

[0261] Generally, the term "3'UTR " refers to a part of the nucleic acid molecule which is located 3' (i.e. "downstream") of an open reading frame and which is not translated into protein. Typically, a 3'UTR is the part of an RNA which is located between the protein coding region (open reading frame (ORF) or coding sequence (CDS)) and the poly(A) sequence of the mRNA. In the context of the present disclosure, the term 3'UTR may also comprise elements, which are not encoded in the template, from which an RNA is transcribed, but which are added after transcription during maturation, e.g. a poly(A) sequence. A 3'UTR of the RNA is not translated into an amino acid sequence. With respect to srRNA, the 3'UTR sequence is generally encoded by the viral genomic RNA, which is transcribed into the respective mRNA during the gene expression process. The genomic sequence is first transcribed into pre-mature mRNA. The pre-mature mRNA is then further processed into mature mRNA in a maturation process.

[0262] "Signal" refers to a suitable nucleic acid sequence which encodes a signal sequence, leader sequence, sorting sequence, in frame with and upstream of the antigenic or coding region. The signal sequence is a short peptide chain, typically found at the N-terminus of a newly synthesized protein, that directs the protein to specific cellular compartments, such as the endoplasmic reticulum (ER), mitochondria, or chloroplasts. Once the protein reaches the target organelle or membrane, the signal sequence is often cleaved off by specific proteases. In an example, the signal encodes a secretion signal and/or a helper epitope.

[0263] "Localization" reference to a suitable nucleic acid sequence which encodes a short peptide segment within a protein that directs the protein to its specific location within the cell, such as the nucleus, mitochondria, endoplasmic reticulum, or other organelles. For example, a nuclear localization signal (NLS) directs proteins to the nucleus, while a mitochondrial targeting sequence guides proteins to mitochondria.

[0264] "Poly(A)" or "Poly(A) tail" refers to the polyadenylation site of the mRNA. The poly(A) tail is a stretch of adenine nucleotides added to the 3' end of eukaryotic messenger RNA (mRNA) molecules during post-transcriptional processing. This modification is catalyzed by the enzyme poly(A) polymerase and plays a critical role in mRNA stability, nuclear export, translation efficiency, and protection from exonucleases. The length of the poly(A) tail can influence gene expression, as longer tails typically enhance translation, while shorter tails may signal mRNA decay. Additionally, the poly(A) tail interacts with poly(A)-binding proteins (PABPs), which help mediate its functions.

[0265] A non-limiting example of the nucleic acid sequences for a multi-specific binding protein according to the disclosure is listed in **Table 6.**

[0266] **Table 6**

SEQ ID NO	Descriptor	Sequence
42	Nucleic acid sequence for tAB0050	atggaattcggcctgtcctggctgtttctggtggctattctgaagggcgtgcagtgc aaggtgcagctggttgaatctggcggaggattggttcagcctggcggctctctga gactgtcttgtgctgcctccggcttcaccttctctagctttggcatgacctgggtccg acaggctcctggcaaaggactggaatgggtgtcctctatctccggctctggctct gataccctgtacgccgattctgtgcggggcagattcaccatctctcgggacaact ccaagaacaccctgtacctgcagatgaactccctgagagccgaggacaccgcc gtgtattactgtaccatcggaggctccctgtctccatctagccagggaacactggt cacagtgtctagtggcggcggtggttctggcggcggatctgaaattgtgctgacc cagtctcctgccacactgtctttgagtcctggcgagagagctaccctgtcctgctct gcttcttcctccgtgggctacatgcactggtatcagcagaagccaggccaggctc ctagactgctgatctacgatacctccaagctggcctctggcatccctgccagattct ctggttctggatctggcaccgacttcaccctgaccatctctagcctggaacctgag gacttcgccgtgtactattgcttccaaggcagcgtgtacccttcacctttggccag ggcaccaagctggaaatcaaaggtggcggtggaagtggtggtggcggatcag gcggaggcggatctcaggttcagctgcaagaatctggacccggcctggtcaag ccttctcagaccctgtctctgacctgtaccgtgtccggcggctctatctctacctcta caatgggcgtcggctggatcagacagcaccctggaaaaggcttggagtggatc ggcttcatttggtgggacgacgacaagcggtacaaccccaacctgaagtccaga gtgaccatgtccgtggacaccagcaagaaccagttctccctgaagctgtcctctgt gaccgccgctgataccgctgtgtactactgcgccagaatggaactgtggtcctac tacttcgactactggggacagggcaccctcgtgacagtttcttcaggcggcggag gtagtggcggaggttctgatatcgtgatgacacagtcccctgacagcctggctgt gtctctgggagagagagccaccatcaactgcaagtcctctcagtctctgctgaac gcccggaccggcaagaactacctggcttggtatcaacaaaagcccggacagcc accaaagctgctcatctactgggcctctaccagagaaagcggcgtgcccgacag attttctggcagcggctctggaacagactttacactgacaatcagctccctgcagg ctgaggatgtggctgtgtattattgcaagcagtcctacagccggcggacctttgga ggcggaacaaaggttgaaatcaaaggcggtggtggcagcggaggcggcgga agcggaggcggaggctctggtggcggaggatctcaagttcagttggtgcagtct ggcgccgaagtgaagaaacctggcgcttctgtgaaggtgtcctgcaaggccag cggcttcaacatcaaggactactacatgcattgggttcgacaagccccaggcca gaggcttgaatggatgggctggatcgacctggaaaacgccaacaccatctacga cgccaagttccagggccgcgtgaccatcacaagagacacctctgcctctaccgc ctacatggaactgagcagcctgagatctgaagatacagccgtctactactgtgcc cgggacgcctacggcagatacttttatgatgtgtggggccaaggcaccctggtta ccgtgtctagctga
43	Nucleic acid sequence for	aagcttgccgccaccatggaatggtcctgggtgttcctgttcttcctgtccgtgacc accggcgtgcactctaaggtgcagctggttgaatctggcggcggattggttcagc

SEQ ID NO	Descriptor	Sequence
	exemplary multi-specific binding protein of SEQ ID: 44	ctggcggatctctgagactgtcttgtgccgcctccggcttcaccttctctagctttgg catgacctgggtccgacaggctcctggcaaaggactggaatgggtgtcctccat ctccggctctggctctgataccctgtacgccgattctgtgcggggcagattcacca tctctcgggacaactccaagaacaccctgtacctgcagatgaactccctgagagc cgaggacaccgccgtgtactactgtaccatcggaggttctctgagcccctctagc cagggcacactggtcacagtttctagcggaggcggaggaagtggcggaggatc tgagattgtgctgacccagtctcctgccacactgtctttgagccctggcgagagag ctaccctgtcctgctctgcctcttcctccgtgggctacatgcactggtatcagcaga agcctggacaggcccctcggctgctgatctacgatacctctaagctggcctctgg catccccgctagattttctggctccggatctggcaccgactttaccctgaccatctc cagcctggaacctgaggacttcgctgtctactactgcttccaaggcagcgtgtac cctttcaccttcggacagggcaccaagctggaaatcaaaggcggtggtggatca ggcggtggcggtagtggtggtggcggttctcaggttcagctgcaagagtctgga cccggcctggtcaagccttctcagaccctgtctctgacctgcaccgtttccggcg gctccatctctacctctaccatgggagtcggctggatcagacagcaccctggaaa aggcctcgagtggatcggcttcatttggtgggacgacgacaagcggtacaaccc caacctgaagtccagagtgaccatgtccgtggacaccagcaagaaccagttctc cctgaagctgtcctccgtgaccgccgctgataccgctgtgtattactgcgcccgg atggaactgtggtcctactacttcgactactggggccagggaaccctcgtgactgt ttcttcaggcggcggaggttccggtggcggatccgatattgtgatgacacagagc cccgacagcctggctgtgtctctgggagaaagagccaccatcaactgcaagtcc tctcagtccctgctgaacgccagaaccggcaagaattacctggcctggtatcaac aaaaacccggccagcctcctaagctgctcatctactgggcctccaccagagaat ccggcgtgcccgatagattctccggcagcggatccggcacagactttacactca caatcagctccctgcaggctgaggacgtggccgtgtattattgcaagcagtccta cagccggcggaccttggaggcggaacaaaggtcgagatcaaaggtggcggt ggcagtggtggcggaggctctggcggaggcggaagtggcggcggtggatctc aagttcagttggtgcagtctggcgccgaagtgaagaaacctggcgcctctgtgaa ggtgtcctgcaaggctagcggcttcaacatcaaggactactacatgcattgggttc gacaagcccctggacagcggctggaatggatgggatggatcgacctggaaaac gccaacaccatctacgacgccaagttccagggcagagtgacaatcaccaggga cacctctgcctccaccgcctacatggaactgagcagcctgagatctgaggataca gcagtctactattgcgccagggacgcctacggccggtacttctatgatgtgtggg gccaaggcaccctggttaccgttagttcttagtgaattc
44	Amino acid sequence for exemplary multi-specific binding protein	MEWSWVFLFFLSVTTGVHSKVQLVESGGGLVQPG GSLRLSCAASGFTFSSFGMTWVRQAPGKGLEWVSS ISGSGSDTLYADSVRGRFTISRDNSKNTLYLQMNSL RAEDTAVYYCTIGGSLSPSSQGTLVTVSSGGGGSGG GSEIVLTQSPATLSLSPGERATLSCSASSSVGYMHW YQQKPGQAPRLLIYDTSKLASGIPARFSGSGSGTDF TLTISSLEPEDFAVYYCFQGSVYPFTFGQGTKLEIKG GGGSGGGGSGGGGSQVQLQESGPGLVKPSQTLSLT CTVSGGSISTSTMGVGWIRQHPGKGLEWIGFIWWD DDKRYNPNLKSRVTMSVDTSKNQFSLKLSSVTAAD

SEQ ID NO	Descriptor	Sequence
		TAVYYCARMELWSYYFDYWGQGTLVTVSSGGGG SGGGSDIVMTQSPDSLAVSLGERATINCKSSQSLLN ARTGKNYLAWYQQKPGQPPKLLIYWASTRESGVP DRFSGSGSGTDFTLTISSLQAEDVAVYYCKQSYSRR TFGGGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQ LVQSGAEVKKPGASVKVSCKASGFNIKDYYMHWV RQAPGQRLEWMGWIDLENANTIYDAKFQGRVTITR DTSASTAYMELSSLRSEDTAVYYCARDAYGRYFYD VWGQGTLVTVSS

[0267] In some non-limiting aspects, a polynucleotide encodes a multi-specific binding protein that has at least about 50%, alternatively at least about 60%, alternatively at least about 65%, alternatively at least about 70%, alternatively at least about 75%, alternatively at least about 80%, alternatively at least about 85%, alternatively at least about 90%, alternatively at least about 93%, alternatively at least about 95%, alternatively at least about 96% alternatively at least about 97%, alternatively at least about 98%, alternatively at least about 99% amino acid sequence identity, or alternatively at least about 100% amino acid sequence identity to amino acid sequence identity to SEQ ID NO: 41 or SEQ ID NO: 44.

[0268] In other non-limiting examples, the polynucleotide that encodes a multi-specific binding protein has at least about 50%, alternatively at least about 60%, alternatively at least about 65%, alternatively at least about 70%, alternatively at least about 75%, alternatively at least about 80%, alternatively at least about 85%, alternatively at least about 90%, alternatively at least about 93%, alternatively at least about 95%, alternatively at least about 96% alternatively at least about 97%, alternatively at least about 98%, alternatively at least about 99%; or alternatively at least about 100% nucleic acid sequence identity to SEQ ID NO: 42 or SEQ ID NO: 43.

[0269] A feature of the universal genetic code is its redundancy. Most amino acids are encoded by more than one codon (the exceptions being the amino acids methionine and tryptophan, which each has only one corresponding codon). Therefore, within the constraints of this degeneracy, a polynucleotide sequence can be altered without affecting the sequence of amino acids in the encoded polypeptide.

[0270] For example, the amino acid alanine has four possible codons (GCT, GCC, GCA, and GCG) that differ from each other in only one nucleotide position, meaning that each time an alanine codon appears within a polynucleotide, the third nucleotide in the codon can be exchanged for another nucleotide without changing the encoded polypeptide.

[0271] Nucleic acid-based therapeutics that combine an nucleic acid-encoded multi-specific binding protein may function as an effective immunotherapy. The prevention or treatment of disease with substances that stimulate the immune response is generally referred to as immunotherapy.

[0272] Any method known in the art for making RNA, including, but not limited to making mRNA, is contemplated herein. Illustrative methods for making RNA include but are not limited to, chemical synthesis and in vitro transcription.

[0273] In certain aspects, the RNA for use in the methods herein is chemically synthesized. Chemical synthesis of relatively short fragments of oligonucleotides with defined chemical structure provides a rapid and inexpensive access to custom-made oligonucleotides of any desired sequence. Whereas enzymes synthesize DNA, RNA, and mRNA only in the 5' to 3' direction, chemical oligonucleotide synthesis does not have this limitation, although it is most often carried out in the opposite, i.e. the 3' to 5' direction. In certain implementations, the process is implemented as solid-phase synthesis using the phosphoramidite method and phosphoramidite building blocks derived from protected nucleosides (A, C, G, and U), or chemically modified nucleosides.

[0274] To obtain the desired oligonucleotide, the building blocks are sequentially coupled to the growing oligonucleotide chain on a solid phase in the order required by the sequence of the product in a fully automated process. Upon the completion of the chain assembly, the product is released from the solid phase to the solution, deprotected, and collected. The occurrence of side reactions sets practical limits for the length of synthetic oligonucleotides (up to about 200 nucleotide residues), because the number of errors increases with the length of the oligonucleotide being synthesized. Products are often isolated by HPLC to obtain the desired oligonucleotides in high purity.

[0275] In certain aspects, RNA is made using in vitro transcription. The terms "RNA in vitro transcription" or "in vitro transcription" relate to a process wherein RNA is synthesized in a

cell-free system (in vitro). DNA, particularly plasmid DNA, is used as template for the generation of RNA and/or mRNA transcripts. RNA may be obtained by DNA-dependent in vitro transcription of an appropriate DNA template, which in certain implementations is a linearized plasmid DNA template. The promoter for controlling in vitro transcription can be any promoter for any DNA-dependent mRNA polymerase. Particular examples of DNA-dependent RNA polymerases are the T7, T3, and SP6 RNA polymerases. A DNA template for in vitro RNA transcription may be obtained by cloning of a nucleic acid, in particular cDNA corresponding to the respective RNA to be in vitro transcribed, and introducing it into an appropriate vector for in vitro transcription, for example into plasmid DNA. In one aspect of the present disclosure, the DNA template is linearized with a suitable restriction enzyme, before it is transcribed in vitro. The cDNA may be obtained by reverse transcription of mRNA or chemical synthesis. Moreover, the DNA template for in vitro RNA synthesis may also be obtained by gene synthesis.

[0276] In some aspects, the nucleic acid-based therapeutic composition is formulated with and/or in communication with a delivery vehicle to form a delivery vehicle complex. A "delivery vehicle" refers to any substance that facilitates, at least in part, the in vivo, in vitro, or ex vivo delivery of a polynucleotide to targeted cells or tissues. Referring to something as a delivery vehicle does not mean that it may not also have therapeutic effects. Delivery vehicles include, but are not limited to, viral vectors and particles such as lentivirus, adenovirus, adeno-associated virus, herpes simplex virus, retrovirus, and the like. Other modalities may also be used such as mRNA, plasmids, and recombinant proteins.

[0277] Thus, the disclosure includes methods for inducing an immune response in a subject in need thereof, comprising administering to the subject an effective amount of the delivery vehicle complex (e.g., formulated as an therapeutic composition) of the disclosure. In some aspects, the administering is by intramuscular, intratumoral, intravenous, intraperitoneal, or subcutaneous delivery. However, all methods that can be used by those skilled in the art to administer a pharmaceutically active agent are contemplated.

G. Therapeutic Activities

[0278] The multi-specific binding protein disclosed herein is designed to simultaneously bind B cells and T cells. Recruitment of T cells facilitates lysis of the B cells involving cytolytic synapse formation and delivery of perforin and granzymes. The engaged T cells are capable of

serial target cell lysis and are not affected by immune escape mechanisms interfering with peptide antigen processing and presentation, or clonal T cell differentiation; see, for example, WO2007042261A2. Accordingly, binding of the multi-specific binding proteins to the target B cells destroys the target cells and/or impairs the progression of B cell related diseases. In specific embodiments in the present invention, the B cell related disease is an autoimmune disease. Any autoimmune disease that would benefit from B cell depletion should be amenable to treatment with an exemplary composition of the present invention, CLN-978 (also referred to as tAB0050 herein throughout).

[0279] In an embodiment, the autoimmune disease treated by CLN-978 is SLE. In an embodiment, the autoimmune disease treated by CLN-978 is RA. In an embodiment, the autoimmune disease treated by CLN-978 is Sjögren's disease.

[0280] In an embodiment, the autoimmune disease treated by CLN-978 is multiple sclerosis (MS). In an embodiment, the autoimmune disease treated by CLN-978 is type 1 diabetes (T1D).

[0281] In an embodiment, the autoimmune disease or disorder treated by CLN-978 is adult dermatomyositis, a rare inflammatory muscle disease characterized by muscle weakness and a distinctive skin rash, often associated with an autoimmune response. In an embodiment, the autoimmune disease or disorder treated by CLN-978 is sine myositis, a subtype of dermatomyositis where patients exhibit characteristic skin symptoms but lack significant muscle involvement. In an embodiment, the autoimmune disease or disorder treated by CLN-978 is juvenile dermatomyositis (JDM), a pediatric autoimmune disease causing muscle inflammation and skin rashes, leading to weakness and potential organ involvement. In an embodiment, the autoimmune disease or disorder treated by CLN-978 is neuromyelitis optica spectrum disorder (NMOSD), a severe autoimmune disorder that primarily affects the optic nerves and spinal cord, often causing blindness and paralysis. In an embodiment, the autoimmune disease or disorder treated by CLN-978 is myasthenia gravis (MG), a neuromuscular autoimmune disorder that leads to weakness in voluntary muscles due to impaired communication between nerves and muscles. In an embodiment, the autoimmune disease or disorder treated by CLN-978 is ANCA-positive vasculitis, a group of autoimmune diseases where antibodies attack blood vessels, leading to inflammation and potential organ damage. In an embodiment, the autoimmune disease or disorder treated by CLN-978 is antiphospholipid syndrome (APS), an autoimmune clotting disorder where

antibodies increase the risk of blood clots, pregnancy complications, and stroke. In an embodiment, the autoimmune disease or disorder treated by CLN-978 is autoimmune cytopenias, a group of disorders where the immune system mistakenly targets and destroys blood cells, leading to anemia, low white blood cell counts, or low platelet levels. Non-limiting examples of autoimmune cytopenias include idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, autoimmune neutropenia and Evans syndrome. In an embodiment, the autoimmune disease or disorder treated by CLN-978 is autoimmune encephalitis, a condition where the immune system attacks the brain, causing inflammation that leads to cognitive, psychiatric, and neurological symptoms. In an embodiment, the autoimmune disease or disorder treated by CLN-978 is pemphigus vulgaris, a rare autoimmune blistering disorder that affects the skin and mucous membranes due to antibodies attacking cell connections.

[0282] Cytotoxicity mediated by multi-specific binding proteins of the disclosure can be measured in various ways in vitro. Effector cells can be e.g., stimulated enriched (human) CD8 positive T cells or unstimulated (human) peripheral blood mononuclear cells (PBMC). If the target cells are of macaque origin or express or are transfected with macaque target cell surface antigen which is bound by the first domain, the effector cells should also be of macaque origin such as a macaque T cell line, e.g., 4119LnPx. The target cells should express CD19, e.g., human or macaque CD19. The target cells can be a cell line (such as CHO) which is stably or transiently transfected with CD19. Alternatively, the target cells can be a cell line naturally expressing CD19, such as B lymphocytes. The effector to target cell (E:T) ratio is usually about 10:1 but can also vary. Killing of the target cells can be measured in a 51Cr-release assay (incubation time of about 18 hours) or in a FACS-based cytotoxicity assay (incubation time of about 48 hours). Other methods of measuring cell death are well-known to the skilled person, such as MTT or MTS assays, ATP-based assays including bioluminescent assays, the sulforhodamine B (SRB) assay, WST assay, clonogenic assay, and the ECIS technology.

[0283] In some embodiments, the cytotoxic activity mediated by the multi-specific binding protein disclosed herein is measured in a cell-based cytotoxicity assay described above. It is represented by the EC50 value, which corresponds to the half maximal effective concentration (concentration of the multi-specific binding protein which induces a cytotoxic response halfway between the baseline and maximum). In some embodiments, the EC50 value of the multi-specific binding proteins is ≦5000 pM, for example, ≦4000 pM, ≦3000 pM, ≦2000 pM, ≦1000 pM,

≦500 pM, ≦400 pM, ≦300 pM, ≦200 pM, ≦100 pM, ≦50 pM, ≦20 pM, ≦10 pM, ≦5 pM, ≦4 pM, ≦3 pM, ≦2 pM, or ≦1 pM.

[0284] It is understood that an EC50 value is generally lower when stimulated/enriched CD8+ T cells are used as effector cells, compared with unstimulated PBMC. It is further understood that the EC50 value is generally lower when the target cells express a high level of the target cell surface antigen compared with a low level of the target antigen. For example, when stimulated/enriched human CD8+ T cells are used as effector cells (and either target cell surface antigen transfected cells such as CHO cells or target cell surface antigen positive human cell lines are used as target cells), the EC50 value of multi-specific binding protein is ≦1000 pM, for example, ≦500 pM, ≦250 pM, ≦100 pM, 50 pM, ≦10 pM, or ≦5 pM. When human PBMCs are used as effector cells, the EC50 value of the multi-specific binding protein is ≦5000 pM, for example, ≦4000 pM, ≦2000 pM, ≦1000 pM, ≦500 pM, ≦200 pM, ≦150 pM, ≦100 pM, ≦50 pM, ≦10 pM, or ≦5 pM. When a macaque T cell line such as LnPx4119 is used as effector cells, and a macaque target cell surface antigen transfected cell line such as CHO cells is used as target cell line, the EC50 value of the multi-specific binding protein is ≦2000 pM, for example, ≦1500 pM, ≦1000 pM, ≦500 pM, ≦300 pM, ≦250 pM, ≦100 pM, ≦50 pM, ≦10 pM, or ≦5 pM.

[0285] Accordingly, in certain embodiments, the EC50 value is measured using stimulated/enriched human CD8+ T cells as effector cells. In some embodiments, the EC50 value is measured using human PBMCs as effector cells. In some embodiments, the EC50 value is measured using a macaque T cell line such as LnPx4119 as effector cells and cells (e.g., CHO cells) engineered to express macaque CD19 as target cells.

[0286] In some embodiments, the multi-specific binding protein of the present disclosure does not induce or mediate lysis of cells that do not express CD19. The term "does not induce lysis" or "does not mediate lysis," or grammatical equivalents thereof, means that the multi-specific binding protein, at a concentration of up to 500 nM, does not induce or mediate lysis of more than 30%, for example, no more than 30%, 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6% or 5% of cells that do not express CD19, whereby lysis of a cell line that expresses CD19 is set to be 100%.

[0287] In some embodiments, a multi-specific binding protein disclosed herein is more effective in killing CD19-expressing cells than the corresponding respective anti-CD19 or anti-CD3 monoclonal antibody at the same molar concentration. For example, the multi-specific

binding protein CLN-978 provides better efficacy than monoclonal antibodies targeting the CD-19 cell surface antigen. In some embodiments, the multi-specific binding protein is more effective in killing CD19-expressing cells than a combination of the corresponding respective anti-CD19 and anti-CD3 monoclonal antibodies each at the same molar concentration.

[0288] The cytotoxic activity of the multi-specific binding protein can be measured in the presence or absence of serum albumin (e.g., HSA). In some embodiments, the cytotoxic activity disclosed above is measured in the absence of serum albumin (e.g., HSA). In some embodiments, the cytotoxic activity disclosed above is measured in substantial absence of serum albumin (e.g., HSA). In some embodiments, the cytotoxic activity disclosed above is measured in the presence of serum albumin (e.g., HSA), for example, in the presence of about 10 mg/mL, 15 mg/mL, 20 mg/mL, 25 mg/mL, 30 mg/mL, 35 mg/mL, 40 mg/mL, 45 mg/mL, or 50 mg/mL serum albumin (e.g., HSA).

[0289] In some embodiments, the multi-specific binding protein of the present disclosure kills CD19-expressing cells with a similar EC50 value in the presence of serum albumin to that in the absence or substantial absence of serum albumin. In some embodiments, the EC50 value of the multi-specific binding protein for killing CD19-expressing cells in the presence of serum albumin is increased by no more than 1.5 fold, 2 fold, 3 fold, 4 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 25 fold, 30 fold, 35 fold, 40 fold, 45 fold, or 50 fold compared to that in the absence or substantial absence of serum albumin. It is understood that the presence of serum albumin (e.g., about 10 mg/mL, 15 mg/mL, 20 mg/mL, 25 mg/mL, 30 mg/mL, 35 mg/mL, 40 mg/mL, 45 mg/mL, or 50 mg/mL serum albumin) may also alter the EC50 value of a multi-specific binding protein nonspecifically. The nonspecific effect can be assessed by comparing the EC50 values of a control protein, which does not contain a serum albumin binding domain, in the presence and absence of serum albumin. In some embodiments, the fold change is offset by the nonspecific effect of serum albumin on a control protein, such as a bispecific protein that binds CD19 and CD3.

H. Construct Size

[0290] In some embodiments, the molecular weight of the multi-specific binding protein is from about 40 kD to about 100 kD. In some embodiments, the molecular weight of the multi-specific binding protein is at least 60 kD, at least 65 kD, at least 70 kD, at least 75 kD, at least 80 kD, at least 85 kD, at least 90 kD, or at least 95 kD. It is understood that smaller size generally

contributes to faster diffusion and tissue penetration, but size reduction may not be as critical for the purpose of treating the indications with substantial presence of CD19-expressing target cells.

[0291] In some embodiments, the molecular weight of the multi-specific binding protein is from about 40 kD to about 90 kD, from about 40 kD to about 80 kD, from about 40 kD to about 70 kD, from about 40 kD to about 60 kD, from about 40 kD to about 50 kD, from about 50 kD to about 100 kD, from about 50 kD to about 90 kD, from about 50 kD to about 80 kD, from about 50 kD to about 70 kD, from about 50 kD to about 60 kD, from about 60 kD to about 100 kD, from about 60 kD to about 90 kD, from about 60 kD to about 80 kD, from about 60 kD to about 70 kD, from about 65 kD to about 100 kD, from about 65 kD to about 90 kD, from about 65 kD to about 80 kD, from about 65 kD to about 70 kD, from about 70 kD to about 100 kD, from about 70 kD to about 90 kD, from about 70 kD to about 80 kD, from about 80 kD to about 100 kD, from about 80 kD to about 90 kD, or from about 90 kD to about 100 kD. In some embodiments, the multi-specific binding protein is lower than 40 kD. In some embodiments, the multi-specific binding protein is about 50 kD – about 90 kD, about 50 kD – about 80 kD, about 50 kD – about 70 kD, about 50 kD – about 60 kD, about 60 kD – about 90 kD, about 60 kD – about 80 kD, about 60 kD – about 70 kD, about 65 kD – about 90 kD, about 65 kD – about 80 kD, about 65 kD – about 70 kD, about 70 kD – about 90 kD, or about 70 kD – about 80 kD.

I. Serum Half-Life

[0292] Fusion proteins have been developed to increase the in vivo half-life of a small protein, particularly an antibody fragment. For example, fusion with a heterodimeric antibody Fc region, such as an Fc with one or more mutations that extend the in vivo half-life, is described in U.S. Patent Application Publication Nos. US20140302037A1, US20140308285A1, and PCT Publication Nos. WO2014144722A2, WO2014151910A1 and WO2015048272A1. An alternative strategy is fusion with human serum albumin (HSA) or an HSA-binding peptide (see, e.g., PCT Publication Nos. WO2013128027A1 and WO2014140358A1). The neonatal Fc receptor (FcRn) appears to be involved in prolonging the life-span of albumin in circulation (see Chaudhury et al. (2003) J. Exp. Med., 3: 315-22). Albumin and IgG bind noncooperatively to distinct sites of FcRn and form a tri-molecular (see id.). Binding of human FcRn to HSA and to human IgG is pH dependent, stronger at acidic pH and weaker at neutral or physiological pH (see id.). This observation suggests that proteins and protein complexes containing albumin, similar to those containing IgG (particularly Fc), are protected from degradation through pH-sensitive

interaction with FcRn (see id.). Using surface plasmon resonance (SPR) to measure the capacity of individual HSA domains to bind immobilized soluble human FcRn, it has been shown that FcRn and albumin interact via the D-III domain of albumin in a pH-dependent manner, on a site distinct from the IgG binding site (see, Chaudhury et al. (2006) Biochemistry 45:4983-90 and PCT Publication No. WO2008068280A1).

[0293] The present disclosure provides multi-specific binding proteins with extended half-life. In some embodiments, the multi-specific binding protein has a serum half-life of at least 24, 36, 48, 60, 72, 84, or 96 hours. In some embodiments, the multi-specific binding protein has a serum half-life of at least about 50 hours. In some embodiments, the multi-specific binding protein has a serum half-life of at least about 100 hours. Methods of measuring serum half-life are known in the art. In some embodiments, the serum half-life is measured in a non-human primate. In some embodiments, the serum half-life is measured in a human.

[0294] In some embodiments, 50 hours after intravenous administration to a subject, the serum concentration of the multi-specific binding protein is at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of the serum concentration of the multi-specific binding protein 1 hour after the administration in said subject.

[0295] In some embodiments, 50 hours after subcutaneous administration to a subject, the serum concentration of the multi-specific binding protein is at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of the serum concentration of the multi-specific binding protein 1 hour after the administration in said subject.

[0296] In some embodiments, the multi-specific binding protein has a serum half-life that is at least 20% longer than a control multi-specific binding protein, wherein the control multi-specific binding protein includes a first domain identical to the first antigen-binding site of the multi-specific binding protein, a second domain identical to the second antigen-binding site of the multi-specific binding protein, but not a third domain identical or substantially identical to the third antigen-binding site of the multi-specific binding protein. In some embodiments, the control multi-specific binding protein is identical to the multi-specific binding protein but for the absence of the half-life extension domain. In some embodiments, the serum half-life of the multi-specific binding protein is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%,

or at least 90% longer than the serum half-life of the control multi-specific binding protein. In some embodiments, the serum half-life of the multi-specific binding protein is longer than the serum half-life of the control multi-specific binding protein by at least 2 fold, at least 3 fold, at least 4 fold, at least 5 fold, at least 6 fold, at least 7 fold, at least 8 fold, at least 9 fold, or at least 10 fold.

[0297] II. METHODS OF PREPARATION

[0298] The antibodies and multi-specific binding proteins described above can be made using recombinant DNA technology well known to a skilled person in the art. For example, one or more isolated polynucleotides encoding the antibody or the multi-specific binding protein can be ligated to other appropriate nucleotide sequences, including, for example, constant region coding sequences, and expression control sequences, to produce conventional gene expression constructs (i.e., expression vectors) encoding the desired antibodies or multi-specific binding proteins. Production of defined gene constructs is within routine skill in the art.

[0299] Nucleic acids encoding desired antibodies or multi-specific binding proteins can be incorporated (ligated) into expression vectors, which can be introduced into host cells through conventional transfection or transformation techniques. Exemplary host cells are E. coli cells, Chinese hamster ovary (CHO) cells, human embryonic kidney 293 (HEK 293) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (e.g., Hep G2), and myeloma cells that do not otherwise produce IgG protein. Transformed host cells can be grown under conditions that permit the host cells to express the genes that encode the antibodies or multi-specific binding proteins.

[0300] Specific expression and purification conditions will vary depending upon the expression system employed. For example, if a gene is to be expressed in E. coli, it is first cloned into an expression vector by positioning the engineered gene downstream from a suitable bacterial promoter, e.g., Trp or Tac, and a prokaryotic signal sequence. The expressed protein may be secreted. The expressed protein may accumulate in refractile or inclusion bodies, which can be harvested after disruption of the cells by French press or sonication. The refractile bodies then are solubilized, and the protein may be refolded and/or cleaved by methods known in the art.

[0301] If the engineered gene is to be expressed in eukaryotic host cells, e.g., CHO cells, it is first inserted into an expression vector containing a suitable eukaryotic promoter, a secretion signal, a poly A sequence, and a stop codon. Optionally, the vector or gene construct may contain enhancers and introns. In embodiments involving fusion proteins comprising an antibody or portion thereof, the expression vector optionally contains sequences encoding all or part of a constant region, enabling an entire, or a part of, a heavy or light chain to be expressed. The gene construct can be introduced into eukaryotic host cells using conventional techniques.

[0302] The antibodies or multi-specific binding protein disclosed herein may comprise a single polypeptide chain. In this instance, a host cell can be transfected with a single vector expressing the polypeptide (e.g., containing an expression control sequence operably linked to a nucleotide sequence encoding the polypeptide). Alternatively, the antibodies or multi-specific binding proteins disclosed herein may comprise two or more polypeptides. In this instance, a host cell can be co-transfected with more than one expression vector, for example, one expression vector expressing each polypeptide. A host cell can also be transfected with a single expression vector that expresses the two or more polypeptides. For example, the coding sequences of the two or more polypeptides can be operably linked to different expression control sequences (e.g., promoter, enhancer, and/or internal ribosome entry site (IRES)). The coding sequences of the two or more polypeptides can also be separated by a ribosomal skipping sequence or self-cleaving sequence, such as a 2A peptide.

[0303] In some embodiments, in order to express an antibody or multi-specific binding protein, an N-terminal signal sequence is included in the protein construct. Exemplary N-terminal signal sequences include signal sequences from interleukin-2, CD-5, IgG kappa light chain, trypsinogen, serum albumin, and prolactin.

[0304] After transfection, single clones can be isolated for cell bank generation using methods known in the art, such as limited dilution, ELISA, FACS, microscopy, or Clonepix. Clones can be cultured under conditions suitable for bio-reactor scale-up and maintained expression of the antibodies or multi-specific binding proteins.

[0305] The antibodies or multi-specific binding proteins can be isolated and purified using methods known in the art including centrifugation, depth filtration, cell lysis, homogenization, freeze-thawing, affinity purification, gel filtration, ion exchange chromatography, hydrophobic interaction exchange chromatography, and mixed-mode chromatography.

[0306] III. PHARMACEUTICAL COMPOSITIONS

[0307] The present disclosure also features pharmaceutical compositions that contain a therapeutically effective amount of the antibodies or multi-specific binding proteins described herein. The composition can be formulated for use in a variety of drug delivery systems. One or more physiologically acceptable excipients or carriers can also be included in the composition for proper formulation. Suitable formulations for use in the present disclosure are found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, Pa., 17th ed., 1985. For a brief review of methods for drug delivery, see, e.g., Langer (Science 249:1527-1533, 1990). In particularly preferred embodiments for the treatment of autoimmune disease, the formulations are formulated for subcutaneous administration.

[0308] In some embodiments, a pharmaceutical composition may contain formulation materials for modifying, maintaining, or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. In such embodiments, suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen-sulfite); buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates or other organic acids); bulking agents (such as mannitol or glycine); chelating agents (such as ethylenediaminetetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin); fillers; monosaccharides; disaccharides; and other carbohydrates (such as glucose, mannose or dextrin); proteins (such as serum albumin, gelatin or immunoglobulins); coloring, flavoring and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counterions (such as sodium); preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide); solvents (such as glycerin, propylene glycol or polyethylene glycol); sugar alcohols (such as mannitol or sorbitol); suspending agents; surfactants or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate, triton, tromethamine, lecithin, cholesterol, tyloxapal); stability enhancing agents (such as sucrose or sorbitol); tonicity enhancing agents (such as alkali metal halides, preferably sodium or potassium chloride, mannitol sorbitol); delivery vehicles; diluents; excipients and/or

pharmaceutical adjuvants (see, Remington's Pharmaceutical Sciences, 18th ed. (Mack Publishing Company, 1990).

[0309] In some embodiments, a pharmaceutical composition may contain nanoparticles, e.g., polymeric nanoparticles, liposomes, or micelles (See Anselmo et al. (2016) BIOENG. TRANSL. MED. 1: 10-29).

[0310] In some embodiments, a pharmaceutical composition may contain a sustained- or controlled-delivery formulation. Techniques for formulating sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads, and depot injections, are also known to those skilled in the art. Sustained-release preparations may include, e.g., porous polymeric microparticles or semipermeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules. Sustained release matrices may include polyesters, hydrogels, polylactides, copolymers of L-glutamic acid and gamma ethyl-L-glutamate, poly (2-hydroxyethyl-inethacrylate), ethylene vinyl acetate, or poly-D(−)-3-hydroxybutyric acid. Sustained release compositions may also include liposomes that can be prepared by any of several methods known in the art.

[0311] Pharmaceutical compositions containing an antibody or a multi-specific binding protein disclosed herein can be presented in a dosage unit form and can be prepared by any suitable method. A pharmaceutical composition should be formulated to be compatible with its intended route of administration. Examples of routes of administration are intravenous (IV), intradermal, inhalation, transdermal, topical, transmucosal, intrathecal, and rectal administration. While in some embodiments, an antibody or a multi-specific binding protein disclosed herein is administered by IV infusion, subcutaneous administration is particularly preferred. Useful formulations can be prepared using methods known in the pharmaceutical art. For example, see Remington's Pharmaceutical Sciences, 18th ed. (Mack Publishing Company, 1990). Formulation components suitable for parenteral administration include a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as EDTA; buffers such as acetates, citrates or phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose.

[0312] For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor ELTM (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). The carrier should be stable under the conditions of manufacture and storage, and should be preserved against microorganisms. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof.

[0313] An intravenous drug delivery formulation may be contained in a syringe, pen, or bag. In some embodiments, the bag is connected to a channel comprising a tube and/or a needle. In some embodiments, the formulation is a lyophilized formulation or a liquid formulation. In some embodiments, the formulation may be freeze-dried (lyophilized) and contained in about 12-60 vials. In some embodiments, the formulation is freeze-dried and 45 mg of the freeze-dried formulation is contained in one vial. In some embodiments, the about 40 mg – about 100 mg of freeze-dried formulation is contained in one vial. In some embodiments, freeze dried formulation from 12, 27, or 45 vials are combined to obtain a therapeutic dose of the protein in the intravenous drug formulation. In some embodiments, the formulation is a liquid formulation and stored as about 250 mg/vial to about 1,000 mg/vial. In some embodiments, the formulation is a liquid formulation and stored as about 600 mg/vial. In some embodiments, the formulation is a liquid formulation and stored as about 250 mg/vial.

[0314] These compositions may be sterilized by conventional sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as-is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the preparations typically will be between 3 and 11, more preferably between 5 and 9 or between 6 and 8, and most preferably between 7 and 8, such as 7 to 7.5. The resulting compositions in solid form may be packaged in multiple single dose units, each containing a fixed amount of the above-mentioned agent or agents. The composition in solid form can also be packaged in a container for a flexible quantity.

[0315] In some embodiments, the present disclosure provides a formulation with an extended shelf life including the protein of the present disclosure, in combination with mannitol, citric acid monohydrate, sodium citrate, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, sodium chloride, polysorbate 80, water, and sodium hydroxide.

[0316] In some embodiments, an aqueous formulation is prepared including the protein of the present disclosure in a pH-buffered solution. The buffer of this disclosure may have a pH ranging from about 4 to about 8, e.g., from about 4.5 to about 6.0, or from about 4.8 to about 5.5, or may have a pH of about 5.0 to about 5.2. Ranges intermediate to the above recited pH's are also intended to be part of this disclosure. For example, ranges of values using a combination of any of the above recited values as upper and/or lower limits are intended to be included. Examples of buffers that will control the pH within this range include acetate (e.g., sodium acetate), succinate (such as sodium succinate), gluconate, histidine, citrate and other organic acid buffers.

[0317] In some embodiments, the formulation includes a buffer system which contains citrate and phosphate to maintain the pH in a range of about 4 to about 8. In some embodiments the pH range is from about 4.5 to about 6.0, or from about pH 4.8 to about 5.5, or in a pH range of about 5.0 to about 5.2. In some embodiments, the buffer system includes citric acid monohydrate, sodium citrate, disodium phosphate dihydrate, and/or sodium dihydrogen phosphate dihydrate. In some embodiments, the buffer system includes about 1.3 mg/ml of citric acid (e.g., 1.305 mg/ml), about 0.3 mg/ml of sodium citrate (e.g., 0.305 mg/ml), about 1.5 mg/ml of disodium phosphate dihydrate (e.g., 1.53 mg/ml), about 0.9 mg/ml of sodium dihydrogen phosphate dihydrate (e.g., 0.86), and about 6.2 mg/ml of sodium chloride (e.g., 6.165 mg/ml). In some embodiments, the buffer system includes 1-1.5 mg/ml of citric acid, 0.25 to 0.5 mg/ml of sodium citrate, 1.25 to 1.75 mg/ml of disodium phosphate dihydrate, 0.7 to 1.1 mg/ml of sodium dihydrogen phosphate dihydrate, and 6.0 to 6.4 mg/ml of sodium chloride. In some embodiments, the pH of the formulation is adjusted with sodium hydroxide.

[0318] A polyol, which acts as a tonicifier and may stabilize the antibody or multi-specific binding protein, may also be included in the formulation. The polyol is added to the formulation in an amount that may vary with respect to the desired isotonicity of the formulation. In some embodiments, the aqueous formulation is isotonic. The amount of polyol added may also be altered with respect to the molecular weight of the polyol. For example, a lower amount of a monosaccharide (e.g., mannitol) is added, compared to a disaccharide (such as trehalose). In some embodiments, the polyol is used in the formulation as a tonicity agent is mannitol. In some embodiments, the mannitol concentration is about 5 to about 20 mg/ml. In some embodiments, the concentration of mannitol is about 7.5 to 15 mg/ml. In some embodiments, the concentration

of mannitol is about 10-14 mg/ml. In some embodiments, the concentration of mannitol is about 12 mg/ml. In some embodiments, the polyol sorbitol is included in the formulation.

[0319] A detergent or surfactant may also be added to the formulation. Exemplary detergents include nonionic detergents such as polysorbates (e.g., polysorbates 20, 80 etc.) or poloxamers (e.g., poloxamer 188). The amount of detergent added is such that it reduces aggregation of the formulated antibody and/or minimizes the formation of particulates in the formulation and/or reduces adsorption. In some embodiments, the formulation may include a surfactant which is a polysorbate. In some embodiments, the formulation may contain the detergent polysorbate 80 or Tween 80. Tween 80 is a term used to describe polyoxyethylene (20) sorbitanmonooleate (see Fiedler, Lexikon der Hifsstoffe, Editio Cantor Verlag Aulendorf, 4th edi., 1996). In some embodiments, the formulation may contain between about 0.1 mg/mL and about 10 mg/mL of polysorbate 80, or between about 0.5 mg/mL and about 5 mg/mL. In some embodiments, about 0.1% polysorbate 80 is added in the formulation.

[0320] In embodiments, the protein product of the present disclosure is formulated as a liquid formulation. The liquid formulation may be presented at a 10 mg/mL concentration in either a USP / Ph Eur type I 50R vial closed with a rubber stopper and sealed with an aluminum crimp seal closure. The stopper may be made of elastomer complying with USP and Ph Eur. In some embodiments, the liquid formulation is diluted with 0.9% saline solution.

[0321] In some embodiments, the liquid formulation of the disclosure is prepared as a 10 mg/mL concentration solution in combination with a sugar at stabilizing levels. In some embodiments the liquid formulation is prepared in an aqueous carrier. In some embodiments, a stabilizer is added in an amount no greater than that which may result in a viscosity that is undesirable or unsuitable for intravenous administration. In some embodiments, the sugar is disaccharides, e.g., sucrose. In some embodiments, the liquid formulation may also include one or more of a buffering agent, a surfactant, and a preservative.

[0322] In some embodiments, the pH of the liquid formulation is set by addition of a pharmaceutically acceptable acid and/or base. In some embodiments, the pharmaceutically acceptable acid is hydrochloric acid. In some embodiments, the base is sodium hydroxide.

[0323] The aqueous carrier of interest herein is one which is pharmaceutically acceptable (safe and non-toxic for administration to a human) and is useful for the preparation of a liquid formulation. Illustrative carriers include sterile water for injection (SWFI), bacteriostatic water

for injection (BWFI), a pH buffered solution (e.g., phosphate-buffered saline), sterile saline solution, Ringer's solution or dextrose solution.

[0324] A preservative may be optionally added to the formulations herein to reduce bacterial action. The addition of a preservative may, for example, facilitate the production of a multi-use (multiple-dose) formulation.

[0325] The antibody or multi-specific binding protein may be lyophilized to produce a lyophilized formulation including the proteins and a lyoprotectant. The lyoprotectant may be sugar, e.g., disaccharides. In some embodiments, the lyoprotectant is sucrose or maltose. The lyophilized formulation may also include one or more of a buffering agent, a surfactant, a bulking agent, and/or a preservative.

[0326] The amount of sucrose or maltose useful for stabilization of the lyophilized drug product may be in a weight ratio of at least 1:2 protein to sucrose or maltose. In some embodiments, the protein to sucrose or maltose weight ratio is of from 1:2 to 1:5. In some embodiments, the pH of the formulation, prior to lyophilization, is set by addition of a pharmaceutically acceptable acid and/or base. In some embodiments the pharmaceutically acceptable acid is hydrochloric acid. In some embodiments, the pharmaceutically acceptable base is sodium hydroxide. Before lyophilization, the pH of the solution containing the protein of the present disclosure may be adjusted between 6 to 8. In some embodiments, the pH range for the lyophilized drug product is from 7 to 8.

[0327] Actual dosage levels of the active ingredients in the pharmaceutical compositions of this disclosure may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

[0328] The specific dose can be a uniform dose for each patient, for example, 50-5,000 mg of protein. Alternatively, a patient's dose can be tailored to the approximate body weight or surface area of the patient. Other factors in determining the appropriate dosage can include the disease or condition to be treated or prevented, the severity of the disease, the route of administration, and the age, sex and medical condition of the patient. Further refinement of the calculations necessary to determine the appropriate dosage for treatment is routinely made by those skilled in the art, especially in light of the dosage information and assays disclosed herein. The dosage can also be determined through the use of known assays for determining dosages used

in conjunction with appropriate dose-response data. An individual patient's dosage can be adjusted as the progress of the disease is monitored. Blood levels of the targetable construct or complex in a patient can be measured to see if the dosage needs to be adjusted to reach or maintain an effective concentration. Pharmacogenomics may be used to determine which targetable constructs and/or complexes, and dosages thereof, are most likely to be effective for a given individual (Schmitz et al., Clinica Chimica Acta 308: 43-53, 2001; Steimer et al., Clinica Chimica Acta 308: 33-41, 2001).

[0329] In general, dosages based on body weight are from about 0.1 μg to about 100 mg per kg of body weight, such as about 0.1 μg to about 100 mg/kg of body weight, about 0.1 μg to about 50 mg/kg of body weight, about 0.1 μg to about 10 mg/kg of body weight, about 0.1 μg to about 1 mg/kg of body weight, about 0.1 μg to about 100 μg/kg of body weight, about 0.1 μg to about 50 μg/kg of body weight, about 0.1 μg to about 10 μg/kg of body weight, about 0.1 μg to about 1 μg/kg of body weight, about 0.1 μg to about 0.1 μg/kg of body weight, about 0.1 μg to about 100 mg/kg of body weight, about 0.1 μg to about 50 mg/kg of body weight, about 0.1 μg to about 10 mg/kg of body weight, about 0.1 μg to about 1 mg/kg of body weight, about 0.1 μg to about 100 μg/kg of body weight, about 0.1 μg to about 10 μg/kg of body weight, about 0.1 μg to about 1 μg/kg of body weight, about 1 μg to about 100 mg/kg of body weight, about 1 μg to about 50 mg/kg of body weight, about 1 μg to about 10 mg/kg of body weight, about 1 μg to about 1 mg/kg of body weight, about 1 μg to about 100 μg/kg of body weight, about 1 μg to about 50 μg/kg of body weight, about 1 μg to about 10 μg/kg of body weight, about 10 μg to about 100 mg/kg of body weight, about 10 μg to about 50 mg/kg of body weight, about 10 μg to about 10 mg/kg of body weight, about 10 μg to about 1 mg/kg of body weight, about 10 μg to about 100 μg/kg of body weight, about 10 μg to about 50 μg/kg of body weight, about 50 μg to about 100 mg/kg of body weight, about 50 μg to about 50 mg/kg of body weight, about 50 μg to about 10 mg/kg of body weight, about 50 μg to about 1 mg/kg of body weight, about 50 μg to about 100 μg/kg of body weight, about 100 μg to about 100 mg/kg of body weight, about 100 μg to about 50 mg/kg of body weight, about 100 μg to about 10 mg/kg of body weight, about 100 μg to about 1 mg/kg of body weight, about 1 mg to about 100 mg/kg of body weight, about 1 mg to about 50 mg/kg of body weight, about 1 mg to about 10 mg/kg of body weight, about 10 mg to about 100 mg/kg of body weight, about 10 mg to about 50 mg/kg of body weight, about 50 mg to about 100 mg/kg of body weight.

[0330] In some aspects, the subject is administered an initial (or priming dose), followed by one or more target (or primary) doses. In an embodiment, the target dose is at least about 2xs greater than the initial dose. In an embodiment, the target dose is at least about 2.5xs greater than the initial dose; alternatively the target dose is at least about 3xs greater than the initial dose; alternatively the target dose is at least about 3.5xs greater than the initial dose; alternatively the target dose is at least about 4xs greater than the initial dose; alternatively the target dose is at least about 4.5xs greater than the initial dose; alternatively the target dose is at least about 5xs greater than the initial dose; alternatively the target dose is at least about 5.5xs greater than the initial dose; alternatively the target dose is at least about 6xs greater than the initial dose; alternatively the target dose is at least about 6.5xs greater than the initial dose; alternatively the target dose is at least about 7xs greater than the initial dose; alternatively the target dose is at least about 7.5xs greater than the initial dose; alternatively the target dose is at least about 8xs greater than the initial dose; alternatively the target dose is at least about 8.5xs greater than the initial dose; alternatively the target dose is at least about 9xs greater than the initial dose; alternatively the target dose is at least about 9.5xs greater than the initial dose; alternatively the target dose is at least about 10xs greater than the initial dose; or alternatively the target dose is at least about 10.5xs greater than the initial dose.

[0331] Doses may be given once or more times daily, weekly, monthly or yearly, or even once every 2 to 20 years. Persons of ordinary skill in the art can easily estimate repetition rates for dosing based on measured residence times and concentrations of the targetable construct or complex in bodily fluids or tissues. Administration of the present disclosure could be intravenous, intraarterial, intraperitoneal, intramuscular, subcutaneous, intrapleural, intrathecal, intracavitary, by perfusion through a catheter or by direct intralesional injection. This may be administered once or more times daily, once or more times weekly, once or more times monthly, and once or more times annually. In some embodiments, administration is intravenous. In some embodiments, administration is subcutaneous.

[0332] **IV. THERAPEUTIC APPLICATIONS**

[0333] It is contemplated that the antibodies or multi-specific binding proteins can be used either alone or in combination with other therapeutic agents.

A. Indications

[0334] The present disclosure provides methods for the treatment or amelioration of an autoimmune disease, whose pathogenesis involves B cells, in a subject in need thereof, the method comprising administration of a multi-specific binding protein or an antibody that binds CD19 disclosed herein in an amount effective to treat one or more symptoms of the disease. In particularly preferred embodiments, the disease is Systemic lupus erythematosus (SLE). SLE is the most common form of lupus in which the immune system attacks its own healthy tissues, resulting in widespread inflammation and tissue damage to joints, skin, brain, lungs, kidneys, and blood vessels. Common symptoms of this disorder include but are not limited to Skin rashes, fatigue, low fevers, pain or swelling of the joints, lung problems, kidney problems, and heart problems, and it often co-exists with conditions such as Lupus nephritis, rheumatoid arthritis, cardiovascular disease, osteoporosis, Sjögren's syndrome, vascular disease, Graves disease, and Hashimoto's thyroiditis. The compositions of the inventions, as more particularly exemplified by CLN-978, are administered to alleviate, reduce, modulate, ameliorate, or eliminate one or more of these symptoms or conditions and results in the improvement of the condition, disease, disorder, and the like, or ameliorating a symptom thereof.

[0335] Peripheral blood B cell count refers to the number of B lymphocytes present in the peripheral blood, the circulating blood outside of the bone marrow and lymphoid tissues. B cells play a crucial role in the immune system by producing antibodies, presenting antigens, and contributing to immune regulation. Measuring peripheral blood B cell counts is a common laboratory test used to evaluate immune function, monitor the effectiveness of therapies (such as monoclonal antibodies targeting B cells), and diagnose or manage conditions like autoimmune diseases, immunodeficiencies, and certain cancers like B-cell lymphomas. The count is typically expressed as a percentage of total lymphocytes or as an absolute number per microliter of blood, measured through techniques like flow cytometry.

[0336] In some aspects the administration of a multi-specific binding protein or an antibody that binds CD19 results in at least about a 75% reduction in peripheral blood B cell count. As used herein the term "reduction in peripheral blood B cell count" refers to a drop in peripheral blood B cell count over time or at a certain time point after the administration of a priming dose, target dose, or primary dose.

[0337] In another aspect, the administration of a multi-specific binding protein or an antibody that binds CD19 results in at least about a 80% reduction in peripheral blood B cell

count. In another aspect, the administration of a multi-specific binding protein or an antibody that binds CD19 results in at least about a 85% reduction in peripheral blood B cell count. In another aspect, the administration of a multi-specific binding protein or an antibody that binds CD19 results in at least about a 90% reduction in peripheral blood B cell count. In another aspect, the administration of a multi-specific binding protein or an antibody that binds CD19 results in at least about a 91% reduction in peripheral blood B cell count. In another aspect, the administration of a multi-specific binding protein or an antibody that binds CD19 results in at least about a 92% reduction in peripheral blood B cell count. In another aspect, the administration of a multi-specific binding protein or an antibody that binds CD19 results in at least about a 93% reduction in peripheral blood B cell count. In another aspect, the administration of a multi-specific binding protein or an antibody that binds CD19 results in at least about a 94% reduction in peripheral blood B cell count. In another aspect, the administration of a multi-specific binding protein or an antibody that binds CD19 results in at least about a 95% reduction in peripheral blood B cell count. In another aspect, the administration of a multi-specific binding protein or an antibody that binds CD19 results in at least about a 96% reduction in peripheral blood B cell count. In another aspect, the administration of a multi-specific binding protein or an antibody that binds CD19 results in at least about a 97% reduction in peripheral blood B cell count. In another aspect, the administration of a multi-specific binding protein or an antibody that binds CD19 results in at least about a 98% reduction in peripheral blood B cell count. In another aspect, the administration of a multi-specific binding protein or an antibody that binds CD19 results in at least about a 99% reduction in peripheral blood B cell count. In another aspect, the administration of a multi-specific binding protein or an antibody that binds CD19 results in at least about a 100% reduction in peripheral blood B cell count.

[0338] B-cell depletion in tissue is critical for effectively managing diseases where B cells play a central role, such as autoimmune disorders, lymphomas, and chronic inflammatory conditions. While circulating B cells in the blood can be targeted relatively easily, B cells residing in tissues such as lymph nodes, bone marrow, and inflamed sites often contribute significantly to disease progression by producing autoantibodies, presenting antigens, and driving inflammatory cascades. Achieving B-cell depletion in these compartments ensures a more comprehensive therapeutic effect, preventing disease recurrence and addressing underlying pathology. Effective depletion in tissue demonstrates a therapeutic's ability to penetrate target sites and engage the

immune system fully, highlighting its potential to provide durable and meaningful clinical outcomes.

[0339] In certain embodiments, administration of administration of a multi-specific binding protein or an antibody that binds CD19 results deep and/or sustained tissue B cell depletion. In some aspects, the deep and/or sustained tissue B cell depletion occurs in the bone marrow of a subject. In another aspect, the deep and/or sustained tissue B cell depletion occurs in the spleen of a subject. In another aspect, the deep and/or sustained tissue B cell depletion occurs in the axial lymph node of a subject. In another aspect, the deep and/or sustained tissue B cell depletion occurs in the mandibular lymph node of a subject.

[0340] Described herein, in some embodiments, are methods of treating an individual in need thereof having SLE, comprising subcutaneously administering to the individual a multi-specific binding protein described herein.

[0341] In particular embodiments, the present invention relates to a method of treating or preventing SLE in a patient in need thereof, the method comprising administering a therapeutically effective amount of CLN-978 or other bispecific TCE composition described herein. In certain embodiments, the method treats mucocutaneous, musculoskeletal and/or renal disease in the patient. The method may reduce the mucocutaneous, musculoskeletal and/or renal flare rate in the patient relative to pre-treatment mucocutaneous, musculoskeletal and/or renal flare rate, respectively.

[0342] The method may cause an improvement in the patient's BILAG-2004 mucocutaneous, renal and/or musculoskeletal organ domain score. The method may improve the patient's SLEDAI-2K mucocutaneous and/or musculoskeletal organ domain score.

[0343] The method may treat cardiorespiratory disease in the patient, optionally wherein the method improves the patient's BILAG-2004 cardiorespiratory organ domain score. The method may treat constitutional disease in the patient, optionally wherein the method improves the patient's BILAG-2004 constitutional organ domain score.

[0344] The method may treat vascular, hematologic, renal and/or cardiorespiratory disease in the patient, optionally wherein the method improves the patient's SLEDAI-2K vascular, hematologic, renal and/or cardiorespiratory disease organ domain score.

[0345] The method may treat or improve rash in the SLE patient such that a measurable, such as, for example, a greater than 50% improvement in the rash in the subject is observed as

compared to pre-treatment levels of rash, optionally wherein the improvement is defined by Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI). The method may resolve rash in the patient. The method may completely resolve SLEDAI-2K-defined rash in the patient.

[0346] The method may treat or prevent arthritis in the patient. The method may completely resolve arthritis in the patient, optionally, wherein the method completely resolves SLEDAI-2K-defined arthritis in the patient.

[0347] The method may lead to an improvement of greater than or equal to 50% in swollen and tender joint count in the patient compared to the pre-treatment swollen and tender joint count in the patient.

[0348] The method may comprise treating or preventing renal disease in the patient that has SLE, wherein the method treats or prevents renal disease in the patient. The patient may have a 24-hour UPCR >0.5 mg/mg pre-treatment, and wherein the method improves the subject's 24-hour UPCR to 0.5 mg/mg.

[0349] The invention also relates to a method of treating SLE in a patient thereof, the method comprising administering a therapeutically effective amount of CLN-978 to the patient, wherein the patient has a baseline CLASI-A ≥10, wherein treatment reduces the patient's CLASI-A ≥50%. The treatment may reduce the patient's CLASI-A by at least week 12 of treatment. The method may lead to a reduction in the patient's CLASI-A, which is maintained for at least 4, 8, 12, 16, 20, 24, 28, 32, 36, or 40 weeks.

[0350] The invention also relates to a method of treating a systemic lupus erythematosus (SLE) patient in need thereof, the method comprising administering a therapeutically effective amount of CLN-978 to the patient, wherein the subject has low complement at baseline compared to a healthy subject, wherein the method reduces SLE disease activity in the patient. Low complement may be defined as less than about 0.1 g/L C4 in the blood and/or less than about 0.9 g/L C3 in the blood.

[0351] The subject may have low C3 and/or C4 complement at baseline compared to a healthy subject. Low C3 may be defined as less than 0.9 g/L in the blood. Low C4 may be defined as less than 0.1 g/L in the blood. The subject may have a SLEDAI-2K score of ≥6, ≥1 A and/or a ≥2 B

[0352] BILAG-2004 organ domain score, and/or a Physician's Global Assessment of ≥1.

[0353] The invention also relates to a method of treating a systemic lupus erythematosus (SLE) patient in need thereof, the method comprising administering a therapeutically effective amount of CLN-978 to the patient, wherein the subject has treatment refractory SLE, and wherein the method reduces SLE disease activity in the subject. The subject may have previously received prior treatment with glucocorticoids, antimalarials and/or immunosuppressants. The subject may have a SLEDAI-2K score of ≥6, ≥1 A and/or a ≥2 B BILAG-2004 organ domain score, and/or a Physician's Global Assessment of ≥1. The subject may have received prior treatment with azathioprine, mizoribine, mycophenolate mofetil, mycophenolic acid, and/or methotrexate.

[0354] Reducing SLE disease activity in the subject may comprise a BILAG-Based Composite Lupus Assessment (BICLA) response. The patient may have moderate to severe SLE.

[0355] **Methods of Measuring End Points for Lupus**

[0356] BILAG-2004 (British Isles Lupus Assessment Group-2004)

[0357] The BILAG-2004 is a translational index with nine organ systems (General, Mucocutaneous, Neuropsychiatric, Musculoskeletal, Cardiorespiratory, Gastrointestinal, Ophthalmic, Renal, and Haematology) that is able to capture the changing severity of clinical manifestations. It has ordinal scales by design and does not have a global score; rather, it records disease activity across the different organ systems at a glance by comparing the immediate past four weeks to the four weeks preceding them. It is based on the principle of physicians' intention to treat and categorizes disease activity into five different levels from A to E:

[0358] Grade A represents very active disease requiring immunosuppressive drugs and/or a prednisone dose of ≥20 mg/day or equivalent.

[0359] Grade B represents moderate disease activity requiring a lower dose of corticosteroids, topical steroids, topical immunosuppressives, antimalarials, or NSAIDs.

[0360] Grade C indicates mild stable disease.

[0361] Grade D implies no disease activity, but the system has previously been affected.

[0362] Grade E indicates no current or previous disease activity.

[0363] Although the BILAG-2004 was developed based on the principle of intention to treat, the treatment has no bearing on the scoring index. Only the presence of active manifestations influences the scoring.

[0364] BICLA (BILAG-Based Composite Lupus Assessment)

[0365] BICLA is a composite index that was originally derived by expert consensus of disease activity indices. BICLA response is defined as (1) at least one gradation of improvement in baseline BILAG scores in all body systems with moderate or severe disease activity at entry (e.g., all A (severe disease) scores falling to B (moderate), C (mild), or D (no activity) and all B scores falling to C or D); (2) no new BILAG A or more than one new BILAG B scores; (3) no worsening of total SLEDAI score from baseline; (4) no significant deterioration (510%) in physicians global assessment; and (5) no treatment failure (initiation of non-protocol treatment).

[0366] A subject is characterized as a BICLA responder if the following criteria are met:

[0367] a) Reduction of all baseline BILAG-2004 A to B/C/D and baseline BILAG-2004 B to C/D, and no BILAG-2004 worsening in other organ systems, as defined by 1 new BILAG-2004 A or more than 1 new BILAG-2004 B item;

[0368] b) No worsening from baseline in SLEDAI-2K as defined as an increase from baseline of ≥0 points in SLEDAI-2K;

[0369] c) No worsening from baseline in the subjects' lupus disease activity defined by an increase ≥0.30 points on a 3-point PGA VAS;

[0370] d) No discontinuation of investigational product or use of restricted medications beyond the protocol allowed threshold before assessment

[0371] CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index Inflammatory Disease Activity)

[0372] The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) was developed in 2005 as a means of specifically tracking cutaneous activity and damage in patients with CLE.

[0373] The CLASI is a simple, single-page tool that separately quantifies skin disease activity and damage in each part of the body. The CLASI features a skin activity summary score (CLASI-A) and damage summary score (CLASI-D). This index has a high inter-rater and intra-rater reliability and is responsive to change when used in adults with SLE. CLASI activity score correlates with the severity of disease: mild, moderate, and severe disease corresponded with CLASI activity score ranges of 0-9 (sensitivity 93%, specificity 78%), 10-20, and 21-70 (sensitivity 80%, specificity 95%), respectively (**Table 7**).

[0374] **Table 7: Disease severity based on the CLASI activity score**

	CLASI activity score range

Mild	0-9
Moderate	10-20
Severe	21-70

[0375] The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) quantifies disease activity and damage in cutaneous lupus erythematosus. It can distinguish between different response levels of treatment, e.g., it is able to detect a specific percentage reduction in activity score from baseline, or can be reported by a mean/median score.

[0376] CLASI is a validated index used for assessing the cutaneous lesions of lupus and consists of 2 separate scores: the first summarizes the inflammatory activity of the disease; the second is a measure of the damage done by the disease. The activity score takes into account erythema, scale/hypertrophy, mucous membrane lesions, recent hair loss, and nonscarring alopecia. The damage score represents dyspigmentation, scarring/atrophy/panniculitis, and scarring of the scalp. Subjects are asked if their dyspigmentation lasted 12 months or longer, in which case the dyspigmentation score is doubled. Each of the above parameters is measured in 13 different anatomical locations, included specifically because they are most often involved in cutaneous lupus erythematosus (CLE). The most severe lesion in each area is measured.

[0377] Modified CLASI (mCLASI) is defined as the activity portions of CLASI that describe skin erythema, scale/hypertrophy, and inflammation of the scalp. Activity of oral ulcers and alopecia without scalp inflammation are excluded from the mCLASI analysis, as are all measures of damage. Clinically meaningful improvement in rash, as measured using mCLASI, is defined by ≥50% decrease in baseline activity score.

[0378] Joint Count

[0379] The swollen and tender joint count is based on left and right shoulder, elbow, wrist, metacarpophalangeal (MCP) 1, MCP2, MCP3, MCP4, MCP5, proximal interphalangeal (PIP) 1, PIP2, PIP3, PIP4, PIPS joints of the upper extremities and left and right knee of the lower extremities.

[0380] Active joint for the joint count assessment is herein defined as a joint with tenderness and swelling only. Each of the 28 joints will then be evaluated separately for tenderness (by palpating the joint) and swelling.

[0381] Proteinuria

[0382] The urine protein/creatinine ratio (UPCR) provides a readout of the amount of blood protein that is passed into the urine. UPCR may be measured in a urine sample collected over a 24-hour period (24-hour UPCR). UPCR may be a spot UPCR, which provides the protein/creatinine ratio measured in a randomly collected urine sample to estimate 24-hour protein excretion.

[0383] Steroids

[0384] Steroids, particularly oral corticosteroids (OCS, glucocorticoids), include prednisone, cortisone, hydrocortisone, methylprednisolone, prednisolone, and triamcinolone.

[0385] Examples of equivalent does are listed in **Table 8.**

[0386] **Table 8: Examples of equivalent doses of oral prednisone**

Oral	Equivalent Dose				
Prednisone	7.5 mg	10 mg	20 mg	30 mg	40 mg
Cortisone	37.5 mg	50 mg	100 mg	150 mg	200 mg
Hydrocortisone	30 mg	40 mg	80 mg	120 mg	160 mg
Methylprednisolone	6 mg	8 mg	16 mg	24 mg	32 mg
Prednisolone	7.5 mg	10 mg	20 mg	30 mg	40 mg
Triamcinolone	6 mg	8 mg	16 mg	24 mg	32 mg

[0387] Described herein, in some embodiments, are methods of treating an individual in need thereof having RA, comprising subcutaneously administering to the individual a multi-specific binding protein described herein.

[0388] RA is a systemic autoimmune disease characterized by inflammatory arthritis and can involve extra-articular manifestations as well (including pericarditis/pleuritis, keratitis, small vessel vasculitis, and pulmonary granulomas). RA, if untreated, is a progressive disease with morbidity due to disability and increased mortality. The etiology includes genetic and environmental factors. It most commonly involves small peripheral joints in a symmetric pattern, and can involve large proximal joints as well. Joint inflammation leads to the thickening of the synovium with invasion and destruction of the cartilage as well as bone erosions.

[0389] While there is currently no cure for RA, the treatment strategy aims to expedite diagnosis and rapidly achieve a low disease activity state (LDAS). There are many composite

scales measuring the disease activity such as the Disease Activity Score using 28 joints (DAS-28), Simplified Disease Activity Assessment Index (SDAI), and Clinical Disease Assessment Index (CDAI). To achieve full suppression of the activity of the disease (clinical remission), rheumatologists need to monitor disease activity continuously and accurately and to adjust the treatment regimen accordingly.

[0390] Current treatment for RA includes symptomatic treatment (such as with nonsteroidal anti-inflammatory drugs [NSAIDs] and corticosteroids) as well as DMARDs. The latter include the conventional synthetic DMARDs, bDMARDs, and novel small molecules (tsDMARDs). Methotrexate is the most commonly used conventional tsDMARD. bDMARDs include TNF-inhibitor, anti-CD20 antibody, IL-6 receptor antibody, and co-stimulation inhibitor (CTLA4-Ig). Recent targeted synthetic molecules include the JAK inhibitors. Despite the increasing number of new drugs and treatment regimes, complete long-term disease remission is not achieved for many patients, and many patients require chronic immunosuppressive treatment, and thus new therapeutic options are required for these high unmet need patients.

[0391] The inflammatory infiltrate in the synovium is complex, and includes macrophages, T cells, B cells, dendritic cells (DCs), neutrophils, and mast cells, which are all involved in the production of chemical mediators. Importantly, the majority of RA patients possess autoantibodies, which can include RF, ACPAs and other AMPAs. Furthermore, B cell/T cell aggregates resembling ectopic lymph nodes are found within the synovium. Finally, recent data strongly supports local plasma cell generation within the synovium.

[0392] Therefore, targeting the B cell lineage is an important and mechanistically deeply rooted therapeutic concept in RA. B cell depletion with the anti-CD20 monoclonal antibody rituximab was demonstrated to be efficacious in the treatment of RA and was approved for treatment, including patients who had an inadequate response to anti-TNF therapy. Remission is only achieved in approximately 30% of patients, and patients who are inadequate responders to other biologics have lower responses. Incomplete responses are likely due, at least in part, to incomplete depletion of tissue-resident B cells. In addition, anti-CD20 does not deplete plasmablasts .

[0393] Recent data support that T cell-redirecting therapies targeting CD19 are potentially efficacious in various autoimmune disorders. Multiple reports characterizing the clinical activity

and safety of CD19 CAR T treatment for severe systemic lupus erythematosus (SLE), systemic sclerosis, and idiopathic inflammatory myositis provide proof-of-concept that therapies inducing deeper depletion of tissue-resident B cell populations can achieve durable, treatment-free remissions in refractory autoimmune disorders. Although refractory to multiple immunosuppressive drug treatments, most patients achieved durable drug-free remission after a single infusion of CD19 CAR T cells. More recent data suggest that a similar immune reset can be achieved with CD19xCD3 TCE treatment. Bucci et al. (2024) showed effective treatment of 6/6 patients with severe RA refractory to multiple disease-modifying therapies using only a brief course of the starting or step-up dose of the CD19xCD3 TCE blinatumomab approved for R/R acute lymphoblastic leukemia. Analysis of synovial biopsies in 3 of the patients revealed that 2 of the patients had a complete depletion of B cells, and the third patient had a reduced B cell count. One patient had abundant CD138+ plasmablasts/plasma cells at baseline which were completely depleted after the blinatumomab treatment. Furthermore, the B cell repopulation after cessation of blinatumomab treatment comprised naïve B cells, raising the possibility of an "immune reset" that could enable long term remission without ongoing immunosuppressive treatment.

[0394] Treatment with CLN-978 thus has the potential to be associated with high treatment response, including disease remission off immunosuppression, in patients with difficult-to-treat rheumatoid arthritis.

[0395] In particular embodiments, the present invention relates to a method of treating or preventing RA in a patient in need thereof, the method comprising administering a therapeutically effective amount of CLN-978 or other bispecific TCE composition described herein.

[0396] Described herein, in some embodiments, are methods of treating an individual in need thereof having Sjögren's disease, comprising subcutaneously administering to the individual a multi-specific binding protein described herein.

[0397] Sjögren's disease (SjD) is a chronic, heterogeneous autoimmune disorder characterized by lymphocytic infiltration of exocrine glands and primarily affecting the salivary and lacrimal glands. SjD is the second most common rheumatic disease and can occur as a primary condition (Primary SjD) or in association with other autoimmune diseases like rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) (Secondary SjD). In the United States, its prevalence is approximately 0.1 per 1,000 people, affecting around 258,000

individuals. Common symptoms include dryness of the eyes, mouth, and skin, but the condition can also cause fatigue, joint pain, and organ involvement in more severe cases. Systemic involvement occurs in 20–70% of patients, potentially leading to organ dysfunction, damage, and increased morbidity, while 15% experience severe, life-threatening disease. Additionally, individuals with SjD face a significantly increased risk of B-cell lymphoma, being 40 times more likely to develop it, with a 5% lifetime risk, particularly for B-cell non-Hodgkin lymphoma (NHL) and mucosa-associated lymphoid tissue (MALT) lymphoma.. The exact cause of SjD is unknown, but a combination of genetic, environmental, and hormonal factors is believed to contribute to its development.

[0398] The four stages of SjD are defined by progressive B-cell hyperactivity, clonal selection, and expansion, which significantly elevate the risk of developing B-cell non-Hodgkin lymphoma (B-NHL). In the early stages, immune system dysregulation leads to chronic inflammation and autoantibody production, gradually promoting B-cell activation. As the disease progresses, clonal selection favors the survival and expansion of autoreactive B cells, increasing the potential for genetic mutations and malignant transformation. Advanced stages are marked by the accumulation of aberrant B-cell clones, ultimately leading to a markedly heightened risk of B-NHL, particularly mucosa-associated lymphoid tissue (MALT) lymphoma.

[0399] There are no currently approved therapies for SjD in the US or Europe, as such, treatment for focuses on symptom management and preventing complications. Artificial tears, saliva substitutes, and medications like pilocarpine and cevimeline are commonly used to alleviate dryness, but they provide only partial relief for many patients. Systemic therapies, such as immunosuppressants or biologics, have shown mixed efficacy and are often reserved for severe, systemic cases. Additionally, the heterogeneity of the disease and difficulty in identifying reliable biomarkers complicate the development of novel therapies..

[0400] The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) is a standardized tool developed by the European League Against Rheumatism (EULAR) to assess systemic disease activity in patients with SjD. It evaluates 12 organ domains, including constitutional, glandular, articular, muscular, pulmonary, renal, hematologic, and central nervous system involvement, among others. Each domain is scored based on the severity of involvement, with higher scores indicating more active disease. ESSDAI is widely used in clinical trials and

research to measure treatment response and disease progression, providing a reliable and reproducible assessment of systemic manifestations beyond just dryness symptoms.

[0401] In some embodiments, a subject with an ESSDAI of 0 does not have SjD and/or they are in remission. In some embodiments, a subject with an ESSDAI of 1, 2, 3, and/or 4, is considered to have a mild form of SjD. In some embodiments, a subject with an ESSDAI of 5, 6, 7, 8, 9, 10, 11, 12, and/or 13, is considered to have a moderate form of SjD. In some embodiments, a subject with an ESSDAI of 14 or greater, is considered to have a severe form of SjD.

[0402] ESSDAI plays a crucial role in guiding treatment decisions and monitoring disease progression in clinical practice. Patients with higher ESSDAI scores often require more aggressive immunosuppressive therapy, such as corticosteroids or biologics, to manage systemic complications. The index helps differentiate between patients with mild, moderate, or severe disease activity, allowing for more personalized treatment approaches. While ESSDAI is an essential tool for assessing systemic involvement, it is often used alongside the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), which focuses on patient-reported symptoms such as dryness, pain, and fatigue, to provide a comprehensive evaluation of disease burden.

[0403] ESSPRI is a simple, patient-reported measure that evaluates three key domains: dryness, fatigue, and pain, each rated on a 0–10 scale. The overall ESSPRI score is calculated as the mean of these three individual scores, providing a comprehensive yet concise assessment of disease burden from the patient's perspective. In some embodiments, a subject with an ESSPRI of 5 or greater has a high symptom burden, while a subject with an ESSPRI of lower than 5 has a low symptom burden.

[0404] In particular embodiments, the present invention relates to a method of treating or preventing SjD in a patient in need thereof, the method comprising administering a therapeutically effective amount of CLN-978 or other bispecific TCE composition described herein.

[0405] In some embodiments, the individual with an autoimmune disease has received at least one other therapy for said autoimmune disease. In some embodiments, the individual has had an inadequate response to such other therapies. In still other embodiments, the individual has had an inadequate response to at least 2 of the following classes of standard therapies for the treatment of SLE at stable doses: oral corticosteroid (OCS), antimalarials, conventional immunosuppressants (e.g. cyclophosphamide, mycofenolic acid or its derivatives, azathioprine,

methotrexate, tacrolimus, cyclopsorin, voclosporin) or monoclonal antibodies (e.g. anifrolumab, belimumab, rituximab, obinutuzumab).

[0406] As discussed herein above, in certain specific embodiments, the present invention relates to the treatment of lupus, such as SLE, RA, and/or SjD wherein the subject has various severities of the disease. In certain such embodiments, the method may comprise steroid sparing in the patient, wherein the dose of the steroid administered to the patient is tapered from a pre-sparing dose at baseline to a post-sparing dose. The post-sparing dose may be 57.5 mg/day prednisone or prednisone equivalent dose. The pre-sparing dose may be 10 mg/day or prednisone equivalent dose. The steroid may comprise a glucocorticoid. The steroid may comprise an oral glucocorticoid. The steroid may be hydrocortisone, mometasone, fluticasone, fluocinolone acetonide, fluocinolone, flurandrenolone acetonide, ciclesonide, budesonide, beclomethasone, deflazacort, flunisolide, beclomethasone dipropionate, betamethasone, betamethasone valerate, methylprednisolone, dexamethasone, prednisolone, cortisol, triamcinolone, clobetasol, clobetasol propionate, clobetasol butyrate, cortisone, corticosterone, clocortolone, dihydroxycortisone, alclometasone, amcinonide, diflucortolone valerate, flucortolone, fluprednidene, fluandrenolone, fluorometholone, halcinonide, halobetasol, desonide, diflorasone, flurandrenolide, fluocinonide, prednicarbate, desoximetasone, fluprednisolone, prednisone, azelastine, dexamethasone 21-phosphate, fludrocortisone, flumethasone, fluocinonide, halopredone, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, hydrocortisone 21-acetate, prednisolone, prednisolone 21-phosphate, clobetasol propionate, triamcinolone acetonide, or a mixture thereof.

[0407] The steroid may comprise prednisone.

B. Combination Therapies

[0408] The methods and compositions described herein can be used alone or in combination with other therapeutic agents and/or modalities. The term administered "in combination," as used herein, is understood to mean that two (or more) different treatments are delivered to the subject during the course of the subject's affliction with the disorder, such that the effects of the treatments on the patient overlap at a point in time. In some embodiments, the delivery of one treatment is still occurring when the delivery of the second begins, so that there is overlap in terms of administration. This is sometimes referred to herein as "simultaneous" or "concurrent delivery." In some embodiments, the delivery of one treatment ends before the

delivery of the other treatment begins. In some embodiments of either case, the treatment is more effective because of combined administration. For example, the second treatment is more effective, e.g., an equivalent effect is seen with less of the second treatment, or the second treatment reduces symptoms to a greater extent, than would be seen if the second treatment were administered in the absence of the first treatment, or the analogous situation is seen with the first treatment. In some embodiments, delivery is such that the reduction in a symptom or other parameter related to the disorder is greater than what would be observed with one treatment delivered in the absence of the other. The effect of the two treatments can be partially additive, wholly additive, or greater than additive. The delivery can be such that an effect of the first treatment delivered is still detectable when the second is delivered.

[0409] In one aspect, the present disclosure provides a method of treating a subject by the administration of a second therapeutic agent in combination with one or more of the multi-specific binding proteins and/or antibodies that bind CD19 disclosed herein.

[0410] It is understood that the antibody or multi-specific binding protein disclosed herein, which is designed to activate T lymphocytes, may cause side effects such as neurotoxicity. Accordingly, in certain embodiments, the second therapeutic agent that can be used in combination with the antibody or multi-specific binding protein comprises an agent that mitigates a side effect of the antibody or multi-specific binding protein, e.g., reduces neurotoxicity. In some embodiments, the second therapeutic agent inhibits T cell trafficking, for example, reduces or inhibits immune cells from crossing the blood-brain barrier. Non-limiting examples of such therapeutic agents include antagonists (e.g., antagonistic antibodies) of adhesion molecules on immune cells (e.g., α4 integrin), such as natalizumab. In some embodiments, the second therapeutic agent increases the internalization of a sphingosine-1-phosphate (SIP) receptor (e.g., S1PR1 or S1PR5), such as fingolimod or ozanimod. In some embodiments, the second therapeutic agent is a nitric oxide synthase (NOS) inhibitor, such as ronopterin, cindunistat, A- 84643, ONO-1714, L-NOARG, NCX-456, VAS-2381, GW-273629, NXN-462, CKD-712, KD- 7040, or guanidinoethyldisulfide. In some embodiments, the second therapeutic agent is an antagonist of CSF1 or CSF1R, such as pexidartinib, emactuzumab, cabiralizumab, LY-3022855, JNJ-40346527, or MCS110. Additional non-limiting examples of the second therapeutic agents include pentosan polysulfate, minocycline, anti-ICAM-1 antibodies, anti-P-selectin antibodies, anti-CD11a antibodies, anti-CD162 antibodies, and anti-IL-6R antibodies (e.g., tocilizumab). In

still other embodiments, the oral corticosteroid (OCS), antimalarials, conventional immunosuppressants (e.g. cyclophosphamide, mycofenolic acid or its derivatives, azathioprine, methotrexate, tacrolimus, cyclopsorin, voclosporin) or monoclonal antibodies (e.g. anifrolumab, belimumab, rituximab, obinutuzumab).

[0411] The amount of the antibody or multi-specific binding protein and additional therapeutic agent and the relative timing of administration may be selected in order to achieve a desired combined therapeutic effect. For example, when administering a combination therapy to a patient in need of such administration, the therapeutic agents in the combination, or a pharmaceutical composition or compositions comprising the therapeutic agents, may be administered in any order such as, for example, sequentially, concurrently, together, simultaneously and the like. Further, for example, an antibody or multi-specific binding protein may be administered during a time when the additional therapeutic agent(s) exerts its prophylactic or therapeutic effect, or vice versa.

[0412] The invention also relates to an injection device comprising the pharmaceutical composition of the invention. The injection device may be a pre-filled syringe (PFS). The injection device may be an accessorized pre-filed syringe (AFPS). The injection device may be an autoinjector.

[0413] The invention also relates to a kit comprising the injection device of the invention and instructions for use. The instructions for use may comprise instructions for subcutaneous administration of the pharmaceutical composition or unit dose to the patient. The instructions for use may specify that the injection device, unit dose and/or pharmaceutical composition are for use in the treatment of SLE. The instructions for use may specify that the injection device, unit dose and/or pharmaceutical composition are for use in the treatment of RA. The instructions for use may specify that the injection device, unit dose and/or pharmaceutical composition are for use in the treatment of SjD. The kit may comprise packaging, wherein the packaging is adapted to hold the injection device and the instructions for use. The instructions for use may be attached to the injection device.

[0414] The instructions for use may specify that the administration of the pharmaceutical composition to the patient treats SLE in the patient. The instructions for use may specify that the administration of the pharmaceutical composition to the patient treats RA in the patient. The instructions for use may specify that the administration of the pharmaceutical composition to the

patient treats SjD in the patient. The instructions may specify that the administration of the pharmaceutical composition to the patient treats mucocutaneous, musculoskeletal and/or renal disease in the patient. The instructions for use may specify that the pharmaceutical composition treats mucocutaneous, musculoskeletal and renal disease in the patient. The instructions for use may specify that the pharmaceutical composition reduces the mucocutaneous, musculoskeletal and/or renal flare rate in the patient relative to pre-treatment mucocutaneous, musculoskeletal and/or renal flare rate, respectively.

[0415] The instructions for use may specify that administration of the pharmaceutical composition to the patient improves the patient's BILAG-2004 mucocutaneous, renal and/or musculoskeletal organ domain score.

[0416] The instructions for use may specify that administration of the pharmaceutical composition to the patient improves the patient's SLEDAI-2K mucocutaneous and/or musculoskeletal organ domain score.

[0417] The instructions for use may specify that that administration of the pharmaceutical composition to the patient treats cardiorespiratory disease in the patient. The instructions for use may specify that the pharmaceutical composition improves the patient's BILAG-2004 cardiorespiratory organ domain score.

[0418] The instructions for use may specify that administration of the pharmaceutical composition to the patient treats constitutional disease in the patient. The instructions for use may specify that the pharmaceutical composition improves the patient's BILAG-2004 constitutional organ domain score.

[0419] The instructions for use may specify that administration of the pharmaceutical composition treats vascular, hematologic, renal and/or cardiorespiratory disease in the patient. The instructions for use may specify that the pharmaceutical composition improves the patient's SLEDAI-2K vascular, hematologic, renal and/or cardiorespiratory disease organ domain score.

[0420] The instructions for use may specify that administration of the pharmaceutical composition treats rash in the patient, optionally there is a $\geq$50% improvement in rash in the subject from pre-treatment levels of rash, optionally wherein the improvement is defined by Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI).

[0421] The instructions for use may specify that administration of the pharmaceutical composition to the patient resolves rash in the patient, and optionally wherein that administration

with the pharmaceutical composition completely resolves SLEDAI-2K-defined rash in the patient. The instructions for use may specify that the administration of the pharmaceutical composition to the patient treats or prevents arthritis in the patient.

[0422] The instructions for use may specify that the administration of the pharmaceutical composition to the patient completely resolves arthritis in the patient, optionally wherein the pharmaceutical composition completely resolves SLEDAI-2K-defined arthritis in the patient.

[0423] The instructions for use may specify that administration of the pharmaceutical composition leads to a ≥50% improvement in swollen and tender joint count in the patient compared to the pre-treatment swollen and tender joint count in the patient, optionally wherein the patient had ≥6 swollen and tender joint count pre-treatment.

[0424] The instructions for use may specify that administration of the pharmaceutical composition to the patient treats or prevents renal disease in the patient.

[0425] The instructions for use may specify that that administration of the pharmaceutical composition to the patient reduces the patient's CLASI-A ≥50%, optionally wherein the patient has a baseline CLASI-A ≥10. The instructions for use may specify that that administration of the pharmaceutical composition to the patient reduces the patient's CLASI-A by at least week 12 of treatment, optionally wherein the reduction in the patient's CLASI-A is maintained for at least 4, 8, 12, 16, 20, 24, 28, 32, 36 or 40 weeks.

[0426] The instructions for use may specify that the patient has low complement at baseline compared to a healthy subject, and that administration of the pharmaceutical composition to the patient reduces SLE disease activity in the patient. The instructions for use may specify that the patient has low complement at baseline compared to a healthy subject, and that administration of the pharmaceutical composition to the patient reduces RA disease activity in the patient. The instructions for use may specify that the patient has low complement at baseline compared to a healthy subject, and that administration of the pharmaceutical composition to the patient reduces SjD disease activity in the patient.

[0427] The instructions for use may specify that the patient has low C3 and/or C4 complement at baseline compared to a healthy subject.

[0428] The instructions for use may specify that the patient has treatment-refractory SLE, and that administration of the pharmaceutical composition to the patient reduces SLE disease activity in the patient.

[0429] The instructions for use may specify that the patient has previously received prior treatment with glucocorticoids, antimalarials and/or immunosuppressants.

[0430] The instructions for use may specify that pretreatment the patient has a SLEDAI-2K score of ≥6, ≥1 A and/or a ≥2 B BILAG-2004 organ domain score, and/or a Physician's Global Assessment of ≥1.

[0431] The instructions for use may specify that the patient has received prior treatment with azathioprine, mizoribine, mycophenolate mofetil, mycophenolic acid, and/or methotrexate.

[0432] The description above describes multiple aspects and embodiments of the disclosure. The patent application specifically contemplates all combinations and permutations of the aspects and embodiments.

[0433] **EXAMPLES**

[0434] The invention now being generally described, will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and is not intended to limit the invention.

[0435] Methods for the preparation of CLN-978 and its uses in treating hematological cancers and non-Hodgkin lymphoma are disclosed in PCT Publication Nos. WO2019237081, WO2021119551, and WO2021119531, and US Provisional Applications 63/494970, 63/464258, 63/511125, 63/581767, 63/605804, 63/494973, and 63/464259 the entirety of each of which is incorporated by reference.

[0436] **Example 1: CLN-978 is safe in patients with relapsed or refractory (R/R) B cell Non-Hodgkin Lymphoma (B-NHL)**

[0437] This Example describes a phase 1, open-label, multi-center, first-in-human, dose escalation, and dose expansion study of CLN-978 to evaluate the safety, PK, PD, and preliminary of efficacy of SC administered CLN-978 for the treatment of R/R B cell non-Hodgkin lymphoma (B-NHL).

[0438] Clinical Safety and Efficacy

[0439] After the first patient treated at the 30 μg dose level experienced a Grade ≥ 2 adverse event, enrollment at that dose level was expanded to three patients as outlined below.

[0440] Patient 1 was a 68-year-old male with relapsed mantle cell lymphoma. Prior treatment included BR followed by maintenance rituximab and lenalidomide, rituximab, dexamethasone,

cytarabine, and cisplatin (R-DHAP), and high-dose chemotherapy and autologous stem cell transplant followed by maintenance rituximab. The patient received the first dose of CLN-978 (30 µg SC) after pre-medication with prednisone, diphenhydramine, famotidine, and acetaminophen. Approximately 26 hours post-dose, the patient experienced a fever to 100.4°F (Grade 1; this was considered unrelated to treatment) accompanied by chills, for which he received an additional dose of acetaminophen. The fever promptly resolved and the work-up for injection was negative. Transient lymphopenia (Grade 3 at nadir 24 hours post-dose consistent with the mechanism of action of CLN-978, was observed beginning C1D2. The remainder of the 48-hour inpatient stay was uneventful. At scheduled outpatient follow-up 96 hours post-dose, the patient was noted to be afebrile but ill-appearing, tremoring but fully oriented (immune effector cell encephalopathy [ICE] score 9/10), and clinically hypovolemic with systolic blood pressure in the 90s. He was admitted to the hospital for volume resuscitation and diagnostic evaluation. Blood pressure promptly normalized after IV fluids, and laboratory testing returned a diagnosis of acute Grade 1 influenza A virus infection (C1D4-C1D6), for which oseltamivir was started and he was discharged from the hospital. A palpable area of mantle cell lymphoma in the right mandible was reported to have resolved from baseline, but there was no clinical or laboratory evidence for tumor lysis or cytokine release syndrome. Tremor (Grade 1; considered unrelated to study treatment) was further treated with corticosteroids, improved after 24 hours, and had resolved by C1D6. Further treatment was deferred for 1 week to allow the patient to complete the 5-day course of oseltamivir and fully recover from influenza. He was readmitted to receive the second dose of CLN-978. Patient also experienced related Grade 2 confusion (C2D14-C2D15) however relatedness with significant usage of corticosteroid cannot be excluded. Other TEAEs included Grade 1 GERD (C1D14-ongoing), Grade 1 intermittent blurred vision (C1D16-ongoing), Grade 2 restlessness (C1D22-ongoing), and Grade 3 vascular access complication (C2D4; patient had a medical history of Grade 3 DVT), all of which were considered unrelated to study treatment. He discontinued treatment after seven doses of CLN-978 due to Grade 2 restlessness and Grade confusion. However, relatedness with significant usage of corticosteroid cannot be excluded. Imaging studies obtained after 2 cycles of therapy demonstrated complete metabolic response.

[0441] Patient 2 was a 25-year old male with diffuse large B-cell lymphoma. Prior treatment included rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)

followed by rituximab maintenance, then rituximab, ifosfamide, carboplatin, and etoposide (R-ICE), and most recently pembrolizumab. The patient received the first dose of CLN-978 (30 μg SC) after pre-medication with dexamethasone, diphenhydramine, famotidine, and acetaminophen. Approximately 10 hours post-dose, the patient developed Grade 1 CRS manifested as fever to 102.9°F (Grade 2) accompanied by dull headache, chills and rigors, for which he was treated with acetaminophen and meperidine. The fever resolved within 2.5 hours without sequelae or recurrence during inpatient monitoring through 48 hours post-dose. Fever to 100.8°F (Grade 1) recurred approximately 50 hours post-dose and again responded to acetaminophen. In both cases, the work-up for infection was negative. Other clinically significant adverse events included transient lymphopenia (Grade 4 at nadir 24 hours post-dose) and leukopenia (max Grade 2 on C1D5-C1D7), consistent with the mechanism of action of CLN-978. Patient also experienced related Grade 1 injection site reaction (C1D13-C2D8), Grade 1 intermittent headaches (C1D2-ongoing), and Grade 1 fatigue (C1D2-C1D6, C1D9-C1D13). Other TEAEs included Grade 1 hyperglycemia (C1D2-C1D3), Grade 1 ALT (C1D2-C1D15), Grade 1 decreased creatinine (C1D3-C1D4), and Grade 1 nausea (C1D10-C1D12), all of which were considered unrelated to study treatment. The patient was re-hospitalized for a second administration of CLN-978, which was uneventful. He discontinued treatment after several doses of CLN-978.

[0442] Patient 3 was a 75-year-old male with relapsed follicular lymphoma. Prior treatment included bendamustine and rituximab (BR) followed by rituximab maintenance, R-CHOP, and lenalidomide and rituximab. The patient received the first dose of CLN-978 (30 μg SC) after pre-medication with dexamethasone, diphenhydramine, famotidine, and acetaminophen. After approximately 48 hours post-dose, the patient developed Grade 1 CRS manifested as fever to 103.1°F (Grade 2), for which he received acetaminophen. The fever promptly resolved, and the work-up for infection was negative. Other TEAEs included related transient lymphopenia (Grade 4 at nadir 24 hours post-dose), consistent with the mechanism of action of CLN-978, observed beginning C1D2 , and Grade 1 pruritus (C1D22-C2D1); and Grade 1 intermittent hypomagnesemia (C1D2-C1D8) and Grade 1 hypocalcemia on C1D4-C1D8, both considered unrelated to study drug. The patient has received 24 weekly doses of CLN-978 in total. Imaging studies obtained after 2 and 4 cycles of therapy demonstrated stable disease; restaging scans after 6 cycles are pending.

[0443] Clinical Pharmacokinetics

[0444] Clinical pharmacokinetic data was limited to patients 1 & 2. These data, provided in **FIG. 5**, show that a preclinical PK model utilized for the B-cell response simulations generally predicts the clinical pharmacokinetic data observed for the two patients administered 30 μg SC on a weekly schedule in the clinical trial.

[0445] Clinical Pharmacodynamics

[0446] Clinical pharmacodynamics data for CLN-978 were generated for each patient. **FIGs. 6A – 6F** are graphs showing B-cell depletion, T-cell activation and cytokine analysis for patients 1, 2, and 3.

[0447] Peripheral blood was tested for the presence of B cells using a quantitative flow cytometry assay (TBNK [T cells, B cells, NK cells] panel). In two out of three B-NHL patients with detectable B cells at baseline (Patients 1 and 2), peripheral B-cell were depleted by 93% and 98% within 96 hours at a dose of 30 μg administered subcutaneously once weekly (QW) and remained low, but detectable, for the remainder of timepoints tested (**FIG. 6A**). Patient 3 had low peripheral blood B cells at baseline and remained low through-out the treatment course. Interestingly, in Patient 2, B-cell lymphocyte counts remained low at the safety follow up visit on Day 149, indicative of persistent peripheral B-cell depletion 90 days after the last dose of CLN-978 was administered on Day 59.

[0448] Peripheral CD3+ cell counts were also assessed using the same TBNK panel. All three patients demonstrated a drop in CD3+ cell counts within four days post-treatment, which was likely caused by a recruitment of peripheral T cells to CD19+ tissues (**FIG. 6B**). Rebound from the initial post-treatment drop in CD3+ event was observed, indicative of T cell redistribution to the periphery.

[0449] Further phenotypic characterization of peripheral T cells demonstrated fluctuations in the overall frequencies of CD4+ (Fig 6C) and CD8+ (**Fig 6D**) T cells across timepoints tested but a return to baseline frequencies in all three patients. T cell activation was examined via the expression of CD69 and PD-1 expression on both CD4 and CD8 T cells (**FIG. 6E**). While there was an increase in the frequency of CD69+ T cells in Patient 1 pre-dose C1D8, expression returned to baseline levels by C1D15. There was large inter-patient variation in PD-1 expression on T cells at baseline between patients but major changes were not observed within patients during the treatment course.

[0450] Patients were also monitored for changes in serum cytokines during the treatment course. Patient 2 showed a transient elevation in levels of IL-6, IL-10, IL-1Rα and MCP-1 at 6 hours after the first dose of CLN-978 (C1D1 6 hours), consistent with the clinical presentation of Grade 1 CRS (**FIG. 6F**). Cytokine levels returned to baseline for the remainder of timepoints assessed. Patients 1 and 3 both showed limited changes in cytokine expression relative to baseline, despite the clinical presentation of Grade 1 CRS in Patient 2 at 48 hrs. post-dose. Of note, there was no expression of IL-1β, IFNγ or IL-2 at any timepoints tested (data not shown).

[0451] Taken together, these data demonstrate B cell depletion in two out of two B-NHL patients with detectable B cells at baseline, as well as T cell mobilization in the periphery of three patients following treatment with CLN-978.

[0452] The clinical observations for the three patients is further summarized in **FIG. 7.**

[0453] Patient 1 was further analyzed. As shown in **FIG. 8,** a 7.4 x 1.7 cm tumor in the left mandibular ramus and adjacent musculature of patient 3 was palpable on physical exam and visible in the oral cavity at pre-treatment baseline. The tumor was no longer appreciable on physical exam at 96 hours following the first dose of CLN-978. The mass reduced in size by 66% (sum of the product of diameters (SPD)) and hypermetabolic disease improved (standard uptake value (SUV)) after 7 doses of CLN-978, consistent with partial response to therapy.

[0454] **Example 2: System Pharmacology PK/PD Modeling**

[0455] A systems pharmacology (SP) model to support initial dose selection of CLN-978 in the clinical trial of Example 1 was modified to support dose selection in a Phase 1 trial in SLE patients. Since B cells play a central role in the pathogenesis of SLE, B cell depletion is a desired outcome for SLE treatment. B cell depletion reduces the autoimmunity characteristics of SLE, reducing disease progression and ideally allowing normal B cells to recover to healthy levels. The existing NHL model was adapted to represent an SLE patient and simulations were performed to predict the duration of B cell depletion in support of Phase 1 studies.

[0456] Model Description:

[0457] The human SP model was developed for CLN-978, a T-cell engager that binds to CD19 on B cells and CD3 on T cells. The model, which was parameterized to describe a non-Hodgkin lymphoma (NHL) patient, was re-parameterized to represent a typical SLE patient. The original model included B-cell depletion in order to appropriately capture the target mediated drug disposition (TMDD) effects on single-dose PK but did not include the recovery of B cells. The

updated model includes both the depletion and recovery kinetics of B cells after CLN-978 treatment (see **FIG. 9**).

[0458] The original CLN-978 model was updated as follows:

[0459] - The tumor compartment, which included malignant B cells, was removed.

[0460] - Recovery of B cells, based on an average half-life of 40 days (Macallan, 2005), was added to the model.

[0461] - The sigmoidal function describing B cell depletion was changed to be dependent on actual trimer per T cell instead of average trimer as modeled previously.

[0462] Previous B cell depletion function:

[0463] **f_kill = k_kill * Avg TpT / (Avg TpT + kill_EC$_{50}$)**

[0464] was updated to:

[0465] **f_kill = k_kill * TpT / (TpT + kill_EC$_{50}$)**

[0466] where **Avg TpT =** trimers formed per number of T cells averaged across the entire simulation; **TpT =** actual trimers formed per number of T cells; **k_kill =** max killing rate; **kill_EC50 = Avg TpT** or **TpT** which gives a half-maximal response. The value of **kill_EC$_{50}$** remained unchanged from the original model = 60.

[0467] Two B-cell proliferation models were explored. The first model (Scenario 1) assumes that B-cell proliferation is guided by a zeroth order process, balanced by a first order death process. The differential equation describing the B-cell rate of change is:

[0468] **dB/dt = kdeath * (B_0 - B),**

[0469] where **dB/dt** is the rate of change of B cells with respect to time, **kdeath** is the death rate of B cells (= log(2) / B-cell half-life of 40 days), **B_0** is the baseline number of B cells in the compartment of interest (central or peripheral, the same equation is used for both compartments), and **B** is the current number of B cells.

[0470] The second model (Scenario 2) assumes that B-cell proliferation is guided by a logistic growth function:

[0471] **dB/dt = kdeath * B * (1 - B/B_0),**

[0472] where all parameters are as described in Scenario 1.

[0473] B-cell depletion kinetics remained the same for Scenario 1 as in the original model, (**k_kill =** log(2) / 1 hour), based on the observed B-cell depletion half-life of 1 - 6 hours in NHL and ALL patients after treatment with blinatumomab (Hijazi, 2018, Nägele, 2021). For Scenario

2, the **k_kill** rate needed to be adjusted. The parameter was estimated manually, so that the maximum level of depletion achieved after a 30 μg single dose in Scenario 2 was consistent with the maximum level of depletion with the same dose with Scenario 1. The estimated **k_kill** corresponded to approximately 14-hour depletion half-life. B-cell depletion for the two Scenarios after the single dose of 30 μg can be seen in **FIGs. 10A** and **10B**. Consistent with the previous model, the SLE model does not distinguish between mature and naive B cells. In addition, there is no intercompartmental distribution of B cells (i.e., B cells turn over in the central (blood) and peripheral (tissue) compartments independently) and B cell dynamics are the same in both compartments. CD19 expression on normal B cells and CD3 expression on T cells was unchanged since numbers in healthy volunteers are assumed to be similar to what is reported in SLE patients. The CD19 dynamics reactions were adjusted to ensure a constant number of CD19 molecules per B cell, regardless of the B-cell dynamics.

[0474] Simulations and analysis:

[0475] The human SLE SP model was used to simulate B-cell depletion following a single dose of CLN-978 administered SC at 30 μg weekly (**FIGs. 10A** and **10B**) and various dose levels, including a priming dose of 10 μg on Day 1 (**FIGs. 11A** and **11B**). Sufficient B cell depletion is conservatively estimated to occur when the number of B cells falls below the threshold of 4 cells/μL. Similarly, recovery, for the purposes of this analysis, is assumed to occur when the number of B cells rises again above 4 cells/μL.

[0476] The results of the model simulations indicate that B-cell depletion following dose levels as low as 10 μg is rapid and decreases below the target threshold of 4 cells/μL within the first days following treatment. However, the duration of B-cell depletion below the target threshold is dependent on the dose and can be extended by multiple doses of CLN-978. As expected, the duration of predicted B-cell depletion in the simulations also depends on the B-cell proliferation model assumed. Overall, the model simulations provide justification for clinical exploration at the currently proposed dose levels and schedules.

[0477] **Example 3: CLN-978 Produces Effective and Efficient B-Cell Depletion**

[0478] In the present example, it is shown that a single dose of CLN-978 achieved rapid and complete B cell depletion. A first patient presented baseline B-cell levels at the periphery at approximately 110 cells/μl prior to the start of treatment. B-cell depletion was observed in this subject within 96 hours at a dose of 30μg administered subcutaneously QW. B-lymphocyte

depletion following the first dose of CLN-978 was sustained until the end of treatment on Day 65 (**FIG. 4**). B-cell lymphocyte counts remained low at the safety follow up visit on Day 149, indicative of persistent B-cell depletion in the periphery 90 days after the last dose of CLN-978 was administered on Day 59.

[0479] Patient 978-0106-003 was lymphopenic and had very low B-cell counts at baseline (~4 cells/μl) that remained low (<4 cell/μl) throughout the course of treatment with CLN-978 (data not shown).

[0480] **Example 4: *In vitro* studies with CLN-978 in PBMCs**

[0481] In vitro studies were conducted in peripheral blood mononuclear cells (PBMCs) to evaluate the potency of CLN-978 in both healthy and diseased cells. PBMCs, which include lymphocytes (T cells, B cells, and NK cells) and monocytes, are critical components of the immune system and are easily isolated from blood samples. Comparing the responses of PBMCs derived from healthy individuals to those from patients with SLE or rheumatoid arthritis (RA) allowed for the evaluation of differential potency and the potential efficacy of CLN-978 in a pathological context. These studies provided valuable insights into mechanisms of action, helping to predict therapeutic outcomes.

[0482] T cell activation was assessed by measuring the induction of CD25 expression on both CD4+ and CD8+ T cells, key markers that indicate early immune response. Cytotoxicity, specifically the ability of T cells to kill target or B cells, was also evaluated to determine the functional capacity of these cells in immune-mediated killing. Additionally, the release of clinically relevant cytokines, such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), was measured, as these cytokines play crucial roles in immune regulation and inflammation. Potency of the immune response was quantified by calculating the EC50, the concentration of the stimulus required to elicit 50% of the maximal observed effect, providing a benchmark for comparing the efficacy of different agents or conditions.

[0483] PBMC from healthy volunteers (n=11) and patients with SLE (n=12) or rheumatoid arthritis (RA) (n=9) were cultured in the presence of CLN-978 for 48 h. T cells (**FIG. 12A**) and B cells (**FIG. 12B**) were analyzed by flow cytometry. Supernatants (**FIG. 12C**) were analyzed using an enzyme-linked immunosorbent assay (ELISA). As shown in **FIGs. 12A-12C,** *in vitro*, CLN-978 induced relatively similar T-cell activation, B-cell killing, and cytokine production in peripheral blood mononuclear cells (PBMCs) from healthy volunteers and patients with SLE or

RA. This shows that there is a strong rationale for broad clinical development in autoimmune diseases that benefit from B-cell depletion, as well as off-the-shelf convenience and a potentially differentiated safety profile.

[0484] Example 5: Sub-ng/mL Sensitivity Achieved for CLN-978 Clinical PK Assay supporting a First in Human Study in Systemic Lupus Erythematosus

[0485] Methods

[0486] Five F(ab')$_2$s and three mAbs targeting either the CD3 or CD19 scFvs were generated using phage display (Bio-Rad) and murine hybridoma (Twist Bioscience) technologies. The CD3 and the CD19 extra cellular domains (ECDs), human CD3 epsilon & CD3 delta heterodimer (CD3 HD) and human CD19 Fc chimera (CD19 Fc) originally used for the B-NHL method, were sourced from AcroBiosystems (CDD-H52W1) and R&D Systems (9269-CD).

[0487] Newly generated reagents were tested with IPCR as this platform supports simultaneous evaluation of multiple reagent combinations in a single run. Samples MRD 1:4, were plated on washed, blocked, capture-reagent coated plates. Incubation and washing were followed by detection using reagents labeled with standard biotin-NHS Ester chemistry, streptavidin conjugated with an Imperacer® DNA tag, and real-time (q) PCR.

[0488] The best performing reagent pair was further evaluated using SIMOA. Assay development utilized EDC activated paramagnetic beads coupled with the CD3 scFv specific capture mAb 1 using standard published SIMOA protocols.

[0489] Biotin coupling of the CD19 scFv specific detection mAb 3, was achieved using standard biotin-NHS Ester chemistry.

[0490] Calibrators and QCs MRD 1:50, and mAb 1 coupled paramagnetic beads were mixed 1:1 with Helper Beads in Super Block and loaded onto the HD-X Analyzer with biotinylated mAb 3, streptavidin beta galactosidase (SBG) and the resorufin β-D-galactopyranoside (RGP) substrate.

[0491] Beads were arrayed against 216,000 femtoliter-sized wells, sealed with oil and imaged. Fluorescence directly proportional to the number of enzymes captured per bead, was analyzed and the average number of enzymes/bead (AEB) imported to Watson LIMS for data regression using a 4PL method with weighting $1/Y^2$.

[0492] Results

[0493] Newly generated F(ab')$_2$s (Bio-Rad) and mAbs (Twist Biosciences), were tested in every combination as capture and detect to optimize the assay's dynamic range, signal – noise (S-N) using IPCR.

[0494] **Table 9** shows the reagent affinities for CLN-978

[0495] **Table 9**

Specificity	Reagent ID	k off (1/s)	KD (nM)
CD3 scFV	mAb 1	1.35E-04	0.30
	mAb 2	5.66E-04	0.86
	Human CD3 epsilon & CD3 delta Heterodimer	6.43E-03	8.00
CD19 scFv	mAb 3	2.34E-04	1.00
	Himan CD19 Fc Chimera	1.39E-05	0.07

[0496] **Table 10** shows S-N for top performing combinations compared with the original assay reagents, CD3 HD and CD19 Fc capture and detect, respectively. Bolded S-N indicates the dynamic range provided by these original reagents: 2.07 at 2.5 ng/mL, and the best performing mAb 1 and mAb 3 reagent pair S-N: 2.49 at 0.156 ng/mL, a 16-fold improvement. As mAbs 1 and 3 provided the best dynamic range, these reagents were selected for assay development using SIMOA.

[0497] **Table 10: Reagent Screening, S-N by IPCR**

Detector, CD19 scFv Specific		mAb 3		CD19 Fc	
Capture, CD3 scFv Specific		mAb 1	mAb 2	mAb 1	CD3 HD
CLN-978 (ng/mL)	5.0	6.79	5.86	4.89	3.42
	2.5	6.00	4.88	3.94	**2.07**
	1.25	4.88	3.82	3.04	1.18
	0.625	4.13	2.84	2.03	.071
	0.313	3.07	2.06	1.42	0.49
	0.156	**2.49**	1.47	0.94	0.49
	0.078	1.52	0.57	0.64	0.41

	0.000	0.00	0.00	0.00	0.00

[0498] Affinity alone did not predict the reagent pair providing the best dynamic range as accessibility and specificity also likely played a key role. Note the CD19 scFv /CD19 ECD KD: 0.074nM, versus the better performing CD19 scFv /mAb 3 KD: 1.04 nM.

[0499] The CLN-978 PK assay quantitative range was established with an 8-point calibration curve 8 – 0.0625 ng/mL and one anchor point below the LLOQ, dilutional linearity (DL), accuracy and precision (A&P), and selectivity in both normal and SLE sera during validation (**Table 11 and FIG. 15**). DL was evaluated from 30.625 - 0.0617 ng/mL.

[0500] **Table 11: Accuracy & Precision**

A&P Summary						
A&P Summary Data		Nominal Concentration (ng/mL)				
		LLOQ	LQC	MQC	HQC	ULOQ
Characteristic	Statistic	0.0625	0.1875	0.7072	6.4000	8.0000
# Results	N	18	18	18	18	18
Accuracy	Mean Bias (% RE)	-6.1	-4.5	-4.3	2.0	3.5
Precision	Intra-assay (%CV)	1.8-8.1	2.6-7.2	2.2-5.8	0.6-5.0	1.1-5.7
	Inter-assay (%CV)	10.9	7.0	6.5	6.1	5.3
Total Error	ABS(%RE)+Interassay (%CV)	17.0	11.5	10.8	8.1	8.8

[0501] **Example 6: Study of CLN-978 by Subcutaneous Injection in Cynomolgus Monkeys**

[0502] CLN-978 was well tolerated in cynomolgus monkeys following the administration of subcutaneous (SC) injections of CLN-978 for four weeks. CLN-978 was administered at single and multiple doses to cynomolgus monkeys at doses ranging from 2 µg/kg to 20 µg/kg. Peripheral B cells were quantified by flow cytometry (**FIG. 13**). Each of the four treatment groups received a 2 µg/kg priming dose on Day 1, following which B cells were rapidly depleted by >90% within 24 hours. Modest B cell recovery was observed before the first target dose of either 6 or 20 µg/kg was administered to Groups 3 and 4 on Day 8 of the study. Immediately following administration of the first target dose, B cells were depleted to below 1% of baseline values, with a subtle dose

response observed between the 6 and 20 μg/kg doses of CLN-978. B cell depletion was sustained below 1% for the Group that received the 20 μg/kg target dose up to at least Day 15 of the study.

[0503] Dose-proportional pharmacokinetic (PK) data shown in **FIG. 16** demonstrates that the concentration of the CLN-978 increases in a predictable and linear manner with increasing doses. This relationship indicates that the CLN-978's absorption, distribution, metabolism, and excretion remain consistent across the dosing range, supporting the reliability of its behavior within the therapeutic window. Such data are critical in establishing that CLN-978 provides a therapeutic benefit, as it confirms that the CLN-978 achieves the necessary systemic exposure at different dose levels to elicit the intended pharmacological effect. Furthermore, dose proportionality provides a foundation for determining optimal dosing regimens, ensuring efficacy and safety across patient populations.

[0504] Dose-proportional pharmacodynamic (PD) data, namely a reduction in peripheral B cells, shown in **FIGs. 17A** and **17B** demonstrates that the therapeutic effect of CLN-978 increases predictably with rising doses, reinforcing its mechanism of action and therapeutic potential. This relationship is observed when incremental increases in dosage result in corresponding enhancements in the biological response or clinical outcomes measured, such as biomarker changes, symptom alleviation, or functional improvements. By showing a clear, dose-dependent relationship, the data supports the hypothesis that the drug's activity is both effective and controllable across a range of doses, providing critical evidence for its efficacy and guiding optimal dosing strategies. Such data is pivotal in clinical development, bridging preclinical findings with clinical results and establishing a foundation for safe and effective use. The data additionally shows a sustained B-cell depletion. As shown in both **FIGs. 17A** and **17B**, several treated monkeys dropped to a peripheral blood B cell count of 0 and stayed at 0 for several days.

[0505] As shown in **FIG. 18,** Human PK modeling provides a predictive framework for understanding how a therapeutic will operate in the body to achieve desired biological outcomes, such as B cell depletion. By integrating PK parameters like drug absorption, distribution, metabolism, and clearance, along with PD relationships, these models estimate CLN-978 concentrations over time and their effect on B cell populations. Predictive modeling uses data from preclinical studies, human PK data, and known relationships between drug exposure and target engagement to forecast the dosing regimens needed for effective B cell depletion. This approach is instrumental in optimizing dose selection, minimizing variability, and ensuring that

therapeutic levels are achieved to maintain sustained B cell suppression, a critical factor in the treatment of autoimmune diseases or cancers. In **FIG. 18,** the PK/PD model developed from the cynomolgus monkey PK/PD data was optimized using the NHL patient data to develop a human PK/PD model for dosing in autoimmune disorders. Model simulations (solid line) of this model show good prediction of the B cell depletion observed in these patients.

[0506] In monkeys administered four weekly subcutaneous doses, a deep and sustained B-cell depletion was observed, affecting both peripheral blood and various tissues. This B-cell depletion extended to key immune sites, including the bone marrow, spleen, and gut-associated lymphoid tissue (GALT), indicating a widespread impact on the B-cell population, as shown in **FIG. 14**. **FIGs. 19A** and **19B** shows a dose-related depletion of B cells was in multiple tissues in a cynomolgus toxicology study one week following four weekly doses of CLN-978 ranging from 0.01 mg/kg to 0.1 mg/kg. **FIGs. 20A** and **20B** shows deep and sustained peripheral blood and bone marrow B cell depletion in a single cynomolgus monkey (animal 4502). These findings suggest that CLN-978 effectively targets B cells across different compartments, highlighting its potential as a therapeutic option for diseases where B-cell modulation is critical. By demonstrating the ability to deplete or regulate B cells not only in peripheral blood but also in tissues and other relevant sites, CLN-978 addresses a key challenge in achieving broad immune modulation. This capability is particularly important in conditions such as autoimmune diseases, B-cell malignancies, and chronic inflammatory disorders, where pathogenic B-cell activity often persists in tissue reservoirs. The observed targeting efficiency supports the therapeutic potential of CLN-978.

[0507] Example 7: A phase 1b, open-label pilot study of fixed duration, subcutaneously administered CLN-978, a CD19XCD3 T cell engager, for the treatment of moderate to severe Systemic Lupus Erythematosus (SLE)

[0508] This following example outlines an open-label study to evaluate the safety and tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of subcutaneously (SC)-administered CLN-978 for the treatment of active Systemic Lupus Erythematosus (SLE). This clinical trial is an exploratory study designed to yield preliminary data about the safety, clinical and biologic efficacy of CLN-978 in SLE patients. Data from this study may inform potential further phase 1 and/or phase 2 studies in SLE patients.

Primary Objective	**Endpoints**
To characterize the safety of fixed duration, subcutaneously administered CLN-978 for the treatment of active Systemic Lupus Erythematosus (SLE)	Incidence of dose-limiting toxicity (DLT) Incidence of all grade AEs and laboratory anomalies Incidence of adverse events of special interest (AESI)
Secondary Objectives	**Endpoints**
To evaluate pharmacokinetics (PK) of subcutaneously administered CLN-978 for the treatment of active SLE	Pharmacokinetic parameters of CLN-978 in the peripheral blood ($t_{1/2}$, C_{max}, AUC)
To evaluate pharmacodynamics (PD) of subcutaneously administered CLN-978 for the treatment of active SLE	Levels of B lymphocytes in the peripheral blood; T-cell activation at the periphery
To evaluate the immunogenicity of subcutaneously administered CLN-978 for the treatment of active SLE	Levels of anti-drug antibodies (ADA)
To evaluate disease related biomarkers following subcutaneously administered CLN-978 for the treatment of active SLE	Autoantibody levels [anti-double stranded DNA (anti-dsDNA); antinuclear (ANA); anti-Smith (anti-SM)] Complement (C3 and C4) levels Erythrocyte Sedimentation Rate (ESR) and C-Reaction Protein (CRP) levels Proinflammatory cytokine levels
To evaluate the preliminary efficacy of subcutaneously administered CLN-978 for the treatment of active SLE at 13, 25, and 49 weeks after starting treatment	Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) Practitioner's Global Assessment (PGA) Definition of Remission in SLE (DORIS)
Exploratory Objectives	**Endpoints**
To evaluate pharmacodynamics (PD) of subcutaneously administered CLN-978 for the treatment of active SLE	Levels of B lymphocytes in the peripheral blood T-cell activation at the periphery
To evaluate disease related biomarkers following subcutaneously administered CLN-978 for the treatment of active SLE	Autoantibody levels [anti-double stranded DNA (anti-dsDNA); antinuclear (ANA); anti-Smith (anti-SM)] Complement (C3 and C4) levels

	Erythrocyte Sedimentation Rate (ESR) and C-Reaction Protein (CRP) levels Proinflammatory cytokine levels

[0509] Patients aged >=18 years with moderate to severe, active SLE (SLEDAI-2K ≥8) will be enrolled. In some cases, the cut off age may be 70.

[0510] This study will be divided into two parts: Part A: Dose Escalation to assess the safety of subcutaneously administered CLN-978 for initial dose expansion and Part B: Dose Expansion to further characterize the safety and preliminary efficacy of CLN-978 for the treatment of active SLE. (See **FIGs. 1** and **2**).

[0511] For each patient, the study will consist of three periods:

[0512] **Screening**: up to 28 days prior to initiation of study treatment

[0513] **Treatment**: Patients will receive SC-administered CLN-978 weekly for four doses.

[0514] **Follow-up**: Patients in all parts of the study will be followed for safety and efficacy for up to one year following the first dose of CLN-978.

[0515] Patients who elect to remain on study after the one-year follow-up period may enter long-term follow-up (LTFU) and undergo intermittent assessments for an additional year.

[0516] A Safety Review Committee (SRC) consisting of Principal Investigators, the Sponsor Medical Monitor, and the Sponsor's representatives will have the responsibility for taking decisions with respect to conduct of the Part A Safety Run-in and whether to initiate Part B Expansion.

[0517] Part A will initially enroll three patients. Two dose levels are planned to be explored: a priming dose of 10 μg on Day 1 and an escalating target dose of 20 μg (Dose Level 1), 30 μg (Dose Level 2), or 45 μg (Dose Level 3) on Day 8 (see **FIG. 1**). As described below, the third dose level may be explored at the discretion of the Safety Review Committee (SRC) if certain safety criteria are satisfied. In the proposed study, escalation of the target dose higher than the 30 μg dose level will only be pursued in absence of Grade ≥2 CRS or neurotoxicity. Alternative priming doses and/or higher target doses may be explored in a subsequent protocol amendment. In Part B, Dose Expansion, this schedule will be further evaluated, as well as an alternative schedule evaluating a priming dose of 10 μg administered on Day 1 and repeat administration of the target dose selected in Part A on Days 8, 15, and 22.

[0518] The primary safety endpoint will be the incidence of Dose Limiting Toxicity (DLT) during the initial 28-day treatment period. For purposes of dose escalation decision-making, DLT is defined as any Grade ≥3 adverse event (AE) or any AE leading to treatment discontinuation. Some laboratory abnormalities (i.e., cytopenias, electrolyte disturbances) and signs or symptoms (i.e., fever, headache) are associated with the mechanism of action of a bispecific T cell engager and/or B cell depletion. Consequently, these events are considered exceptions to the definition of DLT if they are transient and resolve without clinical sequelae. TEAEs unequivocally related to the underlying disease or other extraneous cause will not be considered DLT.

[0519] If 0 of 3 patients experience a DLT, escalation may proceed to the next dose level. If 1 of 3 patients experience a DLT, an additional 3 DLT-evaluable patients will be enrolled. If 1 of 6 patients experience a DLT, escalation may proceed to the next dose level. If ≥ 2 of 3 to 6 patients experience a DLT, the MTD has been exceeded and dose escalation will be discontinued.

[0520] Based upon review of emerging clinical safety, efficacy, and PK/PD data, alternative doses and/or schedules may be explored in a subsequent protocol amendment.

Definition of Dose Limiting Toxicity (DLT)

Any Grade 5 adverse event (AE).
Any Grade 3 or 4 AE with the following exceptions: Grade ≥3 neutropenia lasting ≤ 7 days or unequivocally attributable to underlying disease or extraneous cause; Grade ≥3 thrombocytopenia lasting ≤ 7 days or unequivocally attributable to underlying disease or extraneous cause; Grade 3 or 4 electrolyte abnormalities that are otherwise not associated with clinical complications and respond to medical intervention within 72 hours; Grade 3 fatigue or asthenia; Grade 3 fever; Grade 3 headache that responds to medical intervention within 24 hours; Grade 3 nausea, vomiting, or diarrhea that responds to medical intervention within 72 hours and does not require total parenteral nutrition (TPN), tube feeding, or prolonged hospitalization.

Asymptomatic Grade 3 or 4 laboratory abnormalities may be excluded if they resolve to Grade <2 within 72 hours.
Any AE that results in permanent discontinuation of CLN-978, unless clearly related to the underlying disease.

[0521] During Part B Dose Expansion, the SRC will be convened to review the cumulative rate of DLT after every 3 additional patients are enrolled. In the Schedule 1 cohort, patients will receive a single target dose of CLN-978. In Schedule 2, patients will receive additional target doses of CLN-978 to explore the safety and preliminary efficacy of repeat administration of the target dose. (**FIG. 2**). If the cumulative rate of DLT exceeds 33% or in the event of any Grade 5 AE, further enrollment will be discontinued. Based upon review of emerging clinical safety, efficacy, and PK/PD data, alternative doses and/or schedules may be explored in a subsequent protocol amendment.

[0522] ELIGIBILITY CRITERIA

[0523] Inclusion Criteria

[0524] Age ≥18 years. Patient must understand the purpose of the study and study procedures and can provide signed informed consent. Diagnosis of SLE according to the 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria at least 12 weeks or more prior to screening. Presence of one or more of the following SLE autoantibodies documented within the 12 months prior to screening or during screening: positive ANA (≥1:160); anti dsDNA above the upper limit of normal (ULN); anti-Sm above the ULN.; Active SLE disease, as demonstrated by a SLEDAI-2K total score ≥8 at screening. Inadequate response to at least 2 of the following classes of standard therapies for the treatment of SLE at stable doses: oral corticosteroid (OCS), antimalarials, conventional immunosuppressants (e.g. cyclophosphamide, mycofenolic acid or its derivatives, azathioprine, methotrexate, tacrolimus, cyclopsorin, voclosporin) or monoclonal antibodies (e.g. anifrolumab, belimumab, rituximab, obinutuzumab). If on glucocorticoids, the dose must be ≤ 10 mg daily and stable for 2 weeks prior to screening visit. If on hydroxychloroquine, the maximum allowed dose is 400 mg/day. Males and females with potential for reproduction must agree to practice effective birth control measures (2 approved methods) until 12 weeks after the first dose of CLN-978. For

women of childbearing potential (WOCBP), negative ß-human chorionic gonadotropin (ß-HCG) test at screening and negative urine pregnancy test prior to first administration of CLN-978.

[0525] Laboratory parameters including the following: Absolute lymphocyte count (ALC) $\geq 0.5 \times 10^9$/L; Peripheral CD19+ B cell count ≥25 cells/µL; Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L; Hemoglobin (Hgb) ≥8 g/dL; Platelet count $\geq 75 \times 10^9$/L; Creatinine clearance (Cockcroft-Gault estimated) ≥30 mL/min; Total bilirubin $\leq 1.5 \times$ ULN, except patients with confirmed Gilbert's Syndrome; and AST and ALT $\leq 2.0 \times$ ULN

[0526] Exclusion Criteria

[0527] Active overlap syndrome with mixed connective tissue disease or systemic sclerosis within 12 months prior to screening or during screening. Catastrophic or severe antiphospholipid antibody syndrome within 12 months prior to screening or during screening. Rapidly progressive glomerulonephritis. History of stroke, seizure, dementia, Parkinson's disease, coordination movement disorder, cerebellar diseases, psychosis, paresis, aphasia, and any other neurologic disorder investigator considers would increase the risk for the subject. Evidence of active hepatitis B, hepatitis C infection, HIV, Epstein-Barr virus (EBV), or cytomegalovirus (CMV) infection. Primary immunodeficiency History of splenectomy. Impaired cardiac function or clinically significant cardiac disease. Prior organ allograft. Prior treatment with the following: (i) Cellular therapy (CAR T) or gene therapy product directed at any target, (ii) Receipt of an investigational therapy within 30 days or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment and during the study, (iii) Any anti-CD19 or anti-CD20 therapy such as blinatumumab, obinutuzumab, rixtumab, ocrelizumab, or ofatumumab less than 12 months prior to screening or during screening, (iv) Inhibitors of JAK, Bruton tyrosine kinase, or tyrosine kinase 2, including baracitinib, tofacitinib, upadacitinib, filgotinib, ibrutinib, of fenebrutinib within 30 days prior to screening of during screening, (v) Tacrolimus, cyclosporin, voclosporin, azathioprine, or mycophenolic acid and its derivatives within 30 days prior to screening or during screening, (vii) Cyclophosphamide or a biologic therapy such as but not limited to belimumab, ustekinumab, anifrolumab, secukinumab, or ataticept during 2 months prior to screening or during screening, (viii) Live or attenuated vaccine 28 days prior to screening or during. Known active, clinically significant bacterial, viral, fungal, mycobacterial, parasitic, or other infection, including coronavirus disease of 2019 (COVID-19) infection, at the time of enrollment or within 7 days of the first dose of CLN-978. Previous or concurrent malignancy with

the following exceptions: (i) Adequately treated basal cell or squamous cell carcinoma (adequate wound healing is required prior to screening), (ii) In situ carcinoma of the cervix or breast, treated curatively and without evidence of recurrence for at least 3 years prior to screening, (iii) A primary malignancy which has been completely resected, or treated, and is in complete remission for at least 5 years prior to screening, (iv) Any condition for which, in the opinion of the investigator and/or Sponsor, would not be in the best interest of the patient (i.e., compromise well-being) or that could prevent, limit, or confound any protocol-defined assessment.

[0528] TREATMENT PLAN

[0529] Eligible patients will be enrolled to receive subcutaneously (SC-) administered CLN-978 for a fixed duration administered according to either of two schedules (**FIG. 2**).

[0530] On Day 1 and Day 8, CLN-978 will be administered on an inpatient basis. Patients will be hospitalized for at least 48 hours following CLN-978 administration and should remain hospitalized if there is ongoing fever, hypotension, hypoxia, or ongoing central neurological toxicity greater than Grade 1, or as deemed necessary by the treating physician.

[0531] Prophylaxis for cytokine release syndrome (CRS) with corticosteroids, antihistamines (H1 and H2 blockers), and antipyretics will be administered approximately 1 hour prior to the Day 1 and Day 8 dose of CLN-978. Corticosteroids will also be given at 24- and 48-hours post-dose following Day 1 and Day 8 administration. For subsequent doses (Schedule 2 only), antihistamines and antipyretics will be mandatory prior to each administration, but corticosteroids may be considered in consultation with the Sponsor for patients who experience clinically significant CRS or neurotoxicity following Day 1 or Day 8 dosing.

[0532] Adverse events will be assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (v5.0) with the exception cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). The severity of CRS and ICANS will be graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading Criteria (Lee 2019).

[0533] ICANS and CRS will be collected and reviewed as Adverse Events of Special Interest (AESI).

[0534] Preliminary assessments of clinical response will be measured by changes between baseline (Screening), week 5 (end of treatment; EOT) and weeks 13, 25, and 49 of the following

assessment tools: (i) Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K), (ii) Physician's Global Assessment (PGA), and (iii) Concomitant medication for the treatment of SLE

[0535] Patients will be evaluated against the Definition of Remission in SLE (DORIS) criteria at week 5 (EOT) and weeks 13, 25, and 49.

[0536] Exploratory biomarker response will be measured by changes between baseline (screening), week 5 (EOT), and weeks 13, 25, and 49 of the following parameters, including but not limited to: (i) Changes in anti-dsDNA, ANA, and anti-Sm antibody titers, (ii) Serum complement proteins C3 and C4, (iii) Proinflammatory cytokines, and (iv) T- and B-cell kinetics

[0537] **Example 8: A Phase I, Open-Label Study of CLN-978 in Patients with Treatment-Refractory Rheumatoid Arthritis (RA)**

[0538] This is a Phase 1, open-label study to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and effects on disease activity of subcutaneously (SC)-administered CLN 978 for the treatment of active, treatment-refractory rheumatoid arthritis (RA). The endpoints include incidence and severity of all adverse events (AEs), serious AEs (SAEs), AEs of special interest (AESI), AEs leading to discontinuation, and laboratory abnormalities over 48 weeks.

[0539] The secondary objective include evaluating pharmacokinetics (PK) of CLN-978 in patients with RA; evaluating the PD of CLN-978 with RA; and evaluating the immunogenicity of CLN-978. The endpoints include Serum concentrations of CLN-978; Absolute value and change from baseline of total B lymphocytes in peripheral blood; or Detection of anti-drug antibodies (ADA).

[0540] This is an open-label, two-part study in patients with treatment-refractory RA. Part A is designed to evaluate the safety, PK, PD, and effects on disease activity and identify a candidate dose regimen of CLN-978, and Part B is designed to further evaluate a CLN-978 dosing regimen (selected from Part A). A cohort of patients receiving rituximab treatment in Part B has been included to aid in the interpretation of data from patients treated with CLN-978.

[0541] In both parts of the study, patients aged $\geq$18 years, with at least moderately-active RA (DAS28-ESR $\geq$3.2 and at least one swollen joint), with evidence of B cell-driven disease (i.e., seropositive for RA-associated autoantibodies and/or presence of B cell infiltrate on synovial biopsy), and refractory to at least two disease modifying anti-rheumatic drugs (DMARDS) will

be enrolled. The DMARDs will include targeted synthetic DMARD (tsDMARD) and/or biologic DMARD (bDMARD) with different mechanisms of action (after failing conventional synthetic DMARD therapy, unless contraindicated).

[0542] Background therapy for RA, other than low dose corticosteroid (prednisone equivalent ≤10 mg/day) and antimalarial, will be discontinued during the Screening Period (if not done before the Screening period), as per the exclusion criteria.

[0543] CLN-978 will be administered as described in Part A and Part B. Study visits and assessments will be done according to an established SoA .

[0544] Patients in both parts of the study will be followed for safety, PD, and effects on disease activity for up to 48 weeks following the first dose of CLN-978. Patients who elect to remain in the study after the one-year follow-up period may enter an optional long-term follow-up (LTFU) for an additional 48 weeks.

[0545] The overall study duration for an individual study patient will be up to approximately 24 months, which includes the Screening Period (up to 4 weeks), the Treatment Phase (up to Week 4), the Observation Week (up to Week 48) and the LTFU of an additional 48 weeks.

[0546] To reduce the risks of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), the following will be done:

[0547] In cohorts with more than one dose administration (i.e., planned for Part A Cohort 2 and beyond and for Part B), step-up dosing will be implemented. The first dose will be 10 μg (priming dose), and the next dose (target dose) would be above 10 μg.

[0548] Prednisone or prednisone-equivalent 100 mg orally (PO) x 1 will be given on Day 1 prior to the first treatment with CLN-978, as well as on Day 2 and Day 3. In Cohort 2 and beyond, this will also be given on Day 8 prior to the second (target) dose of CLN-978, as well as on Days 9 and 10. Antihistamine and antipyretic will also be given. Minor adjustment of the premedication regimen may be made according to standard institutional practice in consultation with the Sponsor. The SRC may recommend additional modifications to the premedication regimen (e.g. modifications of the steroid dose and schedule) based on emerging data (safety, PK, and PD).

[0549] Precautions taken also include mandatory 48-hour inpatient stay following the Day 1 and the Day 8 dose administrations, i.e., during the period when the risks of CRS and ICANS are highest, and a sentinel approach to patient dosing throughout the protocol.

[0550] Biopsies of lymph node and synovium are required at baseline and at Week 4, unless medically contraindicated.

[0551] Screening Period: Day -28 to Day -1

[0552] Patients who meet eligibility criteria during the screening period will return to the site for the Day 1 inpatient stay visit.

[0553] Part A

[0554] Part A will evaluate the safety, PK, and PD of CLN-978 in patients with RA. Effects on disease activity will also be assessed. Additionally, this part also aims to identify a candidate dose regimen of CLN-978. Approximately 13 patients will be enrolled.

[0555] Dose-limiting Toxicity (DLT) Periods:

[0556] Cohort 1: There will be a 2-week DLT period. The patient will be administered a single 10 μg dose, and then followed for 2 weeks.

[0557] Cohort 2 and beyond: There will be a 3-week DLT period, consisting of 1 week post the priming dose on Day 1 and 2 weeks post the target dose (the second dose in cohort 2 and beyond) on Day 8.

[0558] After the last patient in a cohort completes the DLT period or terminates early due to an AE, the safety and available PD data will be reviewed by SRC, and the SRC will determine whether to proceed with the next cohort.

[0559] Part B

[0560] Part B will further characterize the safety, PK. PD, and effects on disease activity of this dose regimen of CLN-978 and include assessments of the PD, safety, and effects on disease

activity of rituximab. The data from the cohort of patients treated with rituximab will aid in the interpretation of the data with CLN-978.

[0561] The SRC will use available data on safety, PK, PD, and effects on disease activity from Part A to guide their recommended selection of the dose regimen to be evaluated in Part B. Up to 12 patients per treatment arm (24 patients total) will be enrolled in Part B.

[0562] Dose Limiting Toxicity

[0563] For Part A, the DLT evaluation period is defined as 2 weeks from administration of the CLN-978 dose in cohort 1 (Day 1) and 2 weeks from the administration of the *target dose* (Day 8) in cohorts 2 through 5. This yields a DLT period of 2 weeks in cohort 1 and 3 weeks in cohorts 2 and beyond.

[0564] DLT will be defined by events that are not unequivocally attributable to underlying disease or extraneous cause. The severity of all events (except for CRS and ICANS) will be graded by the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) v5.0. The severity of CRS and ICANS will be graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading criteria.

[0565] DLTs will be reviewed and confirmed by the SRC, and the SRC may also deem an event a DLT even if it does not otherwise meet the protocol-specified criteria.

[0566] Follow-up Phase

[0567] After CLN-978 Treatment Phase in both Parts A and B, patients will enter the Follow-up Phase, commencing from Week 4 visit completion. During this phase, patients will have scheduled clinic visits every 4 weeks until Week 24, and every 8 weeks until Week 48. These visits will involve safety and disease activity assessments, in addition to the collection of biomarker samples.

[0568] A long-term follow-up period (approximately 1 year) will be available for patients who complete the one-year Follow-up Period. If a patient elects to participate, another 4 visits (every 12 weeks) will be performed for up to an additional 48 weeks.

[0569] Inclusion Criteria

[0570] Age ≥18 years at the time of signing the informed consent form. Patient must understand the purpose of the study and study procedures and can provide written informed consent. Documented diagnosis of RA which fulfills the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Classification Criteria

≥12 weeks prior to screening. Evidence of B-cell-driven disease at Screening or previous medical documentation, defined as either (i) seropositivity for RF and/or any AMPA and/or (ii) a synovial biopsy showing B-cell infiltration. Active RA disease, as demonstrated by a DAS28 - ESR ≥3.2 and at least one swollen joint at screening. Inadequate response to at least 2 targeted treatments with different mechanisms. These can include tsDMARD and/or bDMARD, after failing conventional synthetic DMARD (unless contraindicated). If receiving corticosteroid treatments, the dose must be ≤10 mg/day prednisone or prednisone equivalent daily in the 2 weeks prior to initiation of study treatment. Males and females with potential for reproduction must agree to practice effective birth control measures (2 approved methods) during the Treatment and Follow-up periods of the study (48 weeks). For women of childbearing potential (WOCBP), negative ß-human chorionic gonadotropin (ß-HCG) test at screening and urine pregnancy test before CLN-978 dosing.

[0571] Local laboratory assessments must meet the following criteria: Absolute lymphocyte count (ALC) ≥0.5 x 10^9/L; Peripheral CD19+ B cell count ≥25 cells/µL; Absolute neutrophil count (ANC) ≥1.0 x 10^9/L; Hemoglobin (Hgb) ≥8 g/dL; Platelet count ≥75 x 10^9/L. Estimated glomerular filtration rate (eGFR) (based on the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula) ≥30 mL/min/1.73m^2 .Total bilirubin ≤1.5 × ULN, except patients with confirmed Gilbert's Syndrome. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN

[0572] Exclusion Criteria

[0573] Active inflammatory disease other than RA (including but not limited to systemic lupus erythematosus, psoriatic arthritis, spondyloarthropathy, reactive arthritis, systemic sclerosis, dermatomyositis, psoriasis) within 12 months prior to screening or during screening that may interfere with the study assessments. Thyroiditis or secondary Sjogren's syndrome is allowed. History of stroke, seizure, dementia, Parkinson's disease, coordination movement disorder, cerebellar diseases, psychosis, paresis, aphasia, and any other neurologic disorder that the Investigator considers would increase the risk for the patient or confound study results. Evidence of active HCV, human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), or cytomegalovirus (CMV) infection.

[0574] Any evidence of current or past hepatitis B infection (including clinical history with negative current serology); (i) Patients who test positive for hepatitis B surface antigen (hBsAg) and/or hepatitis B core antibody (hBcAb) are ineligible; (ii) Patients who are positive for HCV antibody (HCV Ab) will be reflexively tested for HCV ribonucleic acid (HCV RNA), and only if HCV RNA is negative, they may be considered for enrollment in this study.

[0575] Primary immunodeficiency or history of recurrent infections which, in the opinion of the Investigator could put the patient at undue risk or confound study results. History of splenectomy. Presence of New York Heart Association class III or IV congestive heart failure. Prior organ allograft. Clinical evidence of any other significant unstable or uncontrolled acute or chronic disease not due to RA (i.e., cardiovascular, pulmonary, hematologic, gastrointestinal, hepatic, renal, neurological, malignancy, psychiatric, or infectious disease) which, in the opinion of the Investigator could put the patient at undue risk or confound study results.

[0576] Prior treatment with the following (i) Cellular therapy (e.g. chimeric antigen receptor T cell (CAR-T) or gene therapy product directed at any target; (ii) Receipt of an investigational therapy within 30 days or 5 drug-elimination half-lives (whichever is longer) prior to Day 1 and during the study; (iii) Received any anti-CD19 or anti-CD20 therapy such as blinatumomab, obinutuzumab, rituximab, ocrelizumab, or ofatumumab within 3 months prior to Day 1. Note: In Part B, patients who are considered by the Investigator to have had an inadequate response to prior anti-CD20 treatment will not be assigned to receive rituximab. (iv) Non-biologic DMARD within 14 days prior to Day 1. These include but are not limited to: inhibitors of janus kinase (JAK), Bruton tyrosine kinase, or tyrosine kinase 2 (including baricitinib, tofacitinib, upadacitinib, filgotinib, ibrutinib, or fenebrutinib), mycophenolate, azathioprine, methotrexate, tacrolimus, cyclosporin, voclosporin. (v) Cyclophosphamide or a biologic immunomodulating therapy such as but not limited to anti-tumor necrosis factor (TNF; etanercept, infliximab, adalimumab, golimumab, certolizumab), tocilizumab, abatacept, anakinra, belimumab, ustekinumab, anifrolumab, secukinumab, or atacicept during 2 months prior to Day 1. (vii) Live or live-attenuated vaccines within the 4 weeks prior to the Screening visit or during the Screening Period.

[0577] Known active, clinically significant bacterial, viral, fungal, mycobacterial, parasitic, or other infection, including severe acute respiratory syndrome coronavirus 2

(SARS-CoV-2) infection, within 14 days of the first dose of CLN-978. Active or latent tuberculosis (TB) evidenced by a positive or indeterminant Interferon Gamma Release Assay (IGRA), unless the patient has documented previous completion of TB treatment and no current clinical indication of TB. Previous or concurrent malignancy with the following exceptions as of screening: (i) Adequately treated basal cell or squamous cell carcinoma (adequate wound healing is required). (ii) In situ carcinoma of the cervix or breast, treated curatively and without evidence of recurrence for at least 3 years. (iii) A primary malignancy that has been completely resected or treated and is in complete remission for ≥5 years after the date of latest treatment.

[0578] Example 9: Phase 1b, open-label study of subcutaneously (SC) administered CLN-978 for the treatment of active Sjogren's Disease (SjD).

[0579] This is a Phase 1b, open-label study to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and effect on disease activity of subcutaneously (SC) administered CLN-978 for the treatment of active Sjogren's Disease (SjD). The endpoints include incidence and severity of all adverse events (AEs), serious AEs (SAEs), AEs of special interest (AESI), AEs leading to discontinuation, and laboratory abnormalities over 48 weeks.

[0580] The secondary objective include evaluating pharmacokinetics (PK) of CLN-978 in patients with SjD; evaluating the immunogenicity of CLN-978 in patients with SjD; and evaluating PD-related biomarkers following CLN-978 in patients with SjD. The endpoints include Serum concentrations of CLN-978; Detection of anti-drug antibodies (ADA); or B lymphocyte cell numbers and change from baseline in peripheral blood.

[0581] In order to evaluate the effects on disease activity of CLN-978 in patients with SjD, the inventors will monitor, the Achievement of low disease activity: European League Against Rheumatism Sjogren's Syndrome Disease Activity Index (ESSDAI) <5; Achievement of remission: ESSDAI=0; Achievement of disease response (decrease in ESSDAI ≥3 [MCII], decrease in European League Against Rheumatism Sjogren's Syndrome Patient- Reported Index [ESSPRI] ≥1 or 15% [MCII]); and Absolute value and change from baseline in the following parameters: ESSDAI; Clinical ESSDAI (ClinESSDAI); Stimulated whole salivary flow (SWSF); Schirmer's Test; Composite of Relevant Endpoints for Sjogren's Syndrome (CRESS);

Sjogren Tool for Assessing Response (STAR); Joint count (28 tender/swollen joint counts); and ESSPRI.

[0582] In order to evaluate CLN-978 biomarkers in patients with SjD, the inventors will assess: Levels of naïve and memory B lymphocyte subsets in the peripheral blood and salivary tissue; T cell activation in the peripheral blood and salivary tissue; Autoantibody levels; Immunoglobulin levels; Serum protein and proinflammatory cytokine levels; Levels of antibodies induced by prior vaccinations; and Gene expression in the blood and salivary tissue.

[0583] The study is an open-label, two-part study. Part A is an ascending dose study to evaluate the safety, PK, and PD of CLN-978 in participants with SjD. Efficacy will also be assessed. Candidate dose of CLN-978 will be identified. Alternative priming doses and/or higher target doses may be explored in a subsequent protocol amendment. Part B will further characterize the safety, PK. PD, and effects on disease activity of alternate schedules of CLN-978 at the identified dose.

[0584] Participants with SjD who fulfill the 2016 ACR/EULAR criteria and are positive for anti-SSA/anti-Ro will be eligible. Participants must have active moderate to severe disease (i.e., ESSDAI $\geq$ 5, including disease activity from the following domains: articular, cutaneous, glandular, lymphadenopathy, renal, constitutional, biologic, and/or hematologic) at screening.

[0585] All participants must have inadequate response or loss of response to at least 2 standard-of-care immunosuppressive or biologic therapy (e.g., glucocorticoids, cyclophosphamide, methotrexate, azathioprine, leflunomide, mycophenolic acid derivatives, cyclosporin, rituximab, belimumab, and abatacept)

[0586] Approximately 15-36 participants $\geq$ 18 y/o with moderate to severe SjD will be enrolled. Patients who elect to remain in the study after the one-year follow-up period may enter long-term follow-up (LTFU) for an additional year. The overall study duration for an individual study patient will be up to approximately 25 months.

[0587] Part A will include three dosing cohorts. In Cohort 1, CLN-978 10 μg will be administered as a single dose on Day 1. From Cohort 2 onwards, a priming dose of 10 μg will be administered on Day 1 before administration of an ascending target dose of 20 μg (Cohort 2) or 30 μg (Cohort 3) on Day 8. Each cohort will include 3 to 6 patients. Prednisone-equivalent 100 mg x 1 will be given on Day 1 prior to the first treatment with CLN-978, as well as on Day 2 and Day 3. This will also be given on Day 8 prior to the second (target) dose of CLN-978, as well as

on Day 9 and Day 10. This is done as prophylactic treatment to reduce the risk of the T cell engagement, including cytokine release syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS). A fourth cohort (10 μg on Day 1 and 45 μg on Day 8) may be explored at SRC discretion. Alternative priming doses and/or higher target doses may be explored in a subsequent protocol amendment.

[0588] In each cohort of Part A, a sentinel approach will be followed. The first patient in a cohort must be observed for 48 hours after administration of the last dose (i.e., the dose in Cohort 1, or the second (target) dose in subsequent cohorts) before the second patient in the cohort can be dosed. Following 24-hour observation of this second patient after the last dose, the third patient can be dosed.

[0589] A Safety Review Committee (SRC) consisting of principal Investigators, the Sponsor medical monitor, Sponsor representatives and an external independent expert will use data from Part A to guide their selection of the dose to be evaluated in Part B. In Part B, the identified CLN-978 target dose in Part A will be administered utilizing two dosing schedules. In the Schedule 1 group, patients will receive the 10 μg priming dose on Day 1 followed by a single target dose of on Day 8. In Schedule 2, patients will receive the 10 μg priming dose on Day 1 and the target dose on Day 8, followed by two additional target doses on Day 15 and Day 22. Based upon review of emerging clinical safety, disease activity, and PK/PD data, the SRC may elect to explore a lower dose or discontinue one or both administration schedules. Alternative administration schedules may be explored in a subsequent protocol amendment.

[0590] Patients in all parts of the study will be followed for safety, PK, PD, and effects on disease activity for up to one year following the first dose of CLN-978. Patients who elect to remain in the study after the one-year follow-up period may enter long-term follow-up (LTFU) for an additional year.

[0591] Patients who were treated in Part A and did not experience DLT or discontinue CLN-978 treatment due to AEs are eligible for retreatment at a higher dose or longer schedule in Part B if they otherwise meet eligibility criteria and at least 90 days have passed since the last dose of CLN-978. Patients who discontinue study drug prematurely should complete all study

visits for the remainder of the treatment period and enter the one-year Follow-up Phase. The overall study duration for an individual study patient will be up to approximately 25 months.

[0592] Sample Size: Approximately 15 to 36 patients aged ≥18 years with active moderate to severe SjD will be enrolled.

[0593] Patient Population: All patients must have a diagnosis of SjD, fulfill the 2016 ACR/EULAR criteria, and are positive for anti-SSA/anti-Ro (Shiboski et al, 2017; Appendix A) with active moderate to severe disease activity i.e., ESSDAI ≥5, including disease activity from the following domains: articular, cutaneous, glandular, lymphadenopathy, renal, constitutional, biologic, and/or hematologic) at Screening. Stimulated whole salivary flow ≥0.05 ml/min or unstimulated whole salivary flow ≥0.01 ml/min is required. All patients must also have inadequate response to at least two of the following standard-of-care (SoC) immunosuppressive or biologic therapies: glucocorticoids, cyclophosphamide, methotrexate, azathioprine, leflunomide, mycophenolate derivatives, cyclosporin, rituximab, belimumab, and abatacept. Immunosuppressants and biologics will be discontinued at least 14 days prior to Day 1 (first dose of CLN-978).

[0594] Glucocorticoids may be continued; however, the dose must not be increased during the Screening Period, and the dose must be ≤10 mg/day prednisone (or corticosteroid equivalent) and stable for at least 14 days prior to Day 1. If on an antimalarial, the maximum allowed dose for hydroxychloroquine is 400 mg/day and for chloroquine is 250 mg/day. The dose must be stable for at least 4 weeks prior to the start of the Screening Period and remain stable during this period. All eligibility requirements must be re-confirmed by the Investigator prior to the first dose of CLN-978.

[0595] After completion of the Day 28 assessments (i.e., end of treatment), additional SjD treatment (e.g., immunosuppressant) can be given in accordance with SoC if considered by the Investigator to be required. This initiation of additional treatment should first be discussed with medical monitor.

[0596] Key Inclusion Criteria

[0597] Adults ≥18 years at the time of signing the informed consent form. Participants must understand the purpose of the study and study procedures and can provide signed informed consent. Diagnosis of SjD at least 12 weeks prior to Screening Visit and meet the 2016 ACR/EULAR Classification Criteria for SjD at screening. If a prior salivary biopsy, ocular

surface staining (OSS) test, or van Bijsterveld score were performed, the reports should be obtained for the source documents. Inadequate response or loss of response to at least 2 standard-of-care immunosuppressive or biologic therapies (e.g., glucocorticoids, cyclophosphamide, methotrexate, azathioprine, leflunomide, mycophenolate derivatives, cyclosporin, rituximab, belimumab, and abatacept). Have a positive anti-Sjogren's syndrome-associated antigen A (anti-SSA/anti-Ro) at Screening. Have active moderate to severe disease (i.e., ESSDAI ≥5, including disease activity from the following domains: articular, cutaneous, glandular, lymphadenopathy, renal, constitutional, biologic, and/or hematologic) at Screening. Note: Participant may have activity in the remaining 4 domains (i.e., central nervous system, peripheral nervous system, pulmonary system, and muscular system); However, these domains scores will not be counted towards eligibility. On the other hand, the complete ESSDAI (12 domains) will be used to assess disease activity in the study.

[0598] Stimulated whole salivary flow ≥0.05 ml/min or unstimulated whole salivary flow ≥0.01 ml/min at Screening. If on glucocorticoids, the dose must not be increased during the Screening Period and must be ≤10 mg prednisone (or corticosteroid equivalent dose daily [Appendix C]) and at stable dose at least 14 days prior to Day 1. If on an antimalarial, the maximum allowed dose for hydroxychloroquine is 400 mg/day and for chloroquine is 250 mg/day. The dose must be stable for at least 4 weeks prior to the Screening visit and remain stable during the Screening period.

[0599] Males and females with potential for reproduction must agree to practice effective birth control measures until 12 weeks after the last dose of study drug. One of the approved methods must be a highly effective form of contraception (i.e., failure rate < 1% per year when used consistently and correctly). For women of childbearing potential (WOCBP), negative ß-human chorionic gonadotropin (ß HCG) blood test at screening and negative urine pregnancy test on Day 1 prior to first administration of CLN 978.

[0600] Laboratory parameters including the following: Absolute lymphocyte count (ALC) ≥0.5 x 10^9/L; Peripheral CD19+ B cell count ≥25 cells/µL; Absolute neutrophil count (ANC) ≥1.0 x 10^9/L; Hemoglobin (Hgb) ≥8 g/dL; Platelet count ≥75 x 10^9/L; Creatinine clearance (Cockcroft-

Gault estimated) ≥30 mL/min; Total bilirubin ≤1.5 × ULN, except patients with confirmed Gilbert's Syndrome; AST and ALT ≤2.0 × ULN.

[0601] Key Exclusion Criteria

[0602] Concomitant autoimmune disease (e.g. systemic lupus erythematosus, rheumatoid arthritis, idiopathic inflammatory myopathies, systemic sclerosis, autoimmune hepatitis, and sarcoidosis). Patients with Hashimoto's thyroiditis or celiac disease may be included if treated and well controlled according to the Investigator. Participants with active fibromyalgia with pain symptoms or signs that would interfere with joint assessment or requiring adjustment of medications within 3 months before Screening to control symptoms. Participants with fibromyalgia that is well controlled may be considered. Rapidly progressive glomerulonephritis (e.g., impending need for renal replacement therapy), and/or urine protein/creatinine >3 mg/mg (339 mg/mmol). Active severe neuropsychiatric/CNS manifestations of SjD. History of stroke, seizure, dementia, Parkinson's disease, coordination movement disorder, cerebellar diseases, psychosis, paresis, aphasia, and any other neurologic disorder that the Investigator considers would put the patient at undue risk or confound study results.

[0603] Evidence of hepatitis B, hepatitis C (HCV) infection, human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), or cytomegalovirus (CMV) infection. (i) Patients who test positive for hepatitis B surface antigen [hBsAg] and/or hepatitis B core Ab are ineligible; (ii) Patients who are positive for hepatitis C virus antibody (HCV Ab) will be reflex tested for HCV ribonucleic acid (HCV RNA) and only if HCV RNA is negative, they may be considered for enrollment in this study.

[0604] Primary immunodeficiency or history of recurrent infections. Participants with IgA deficiency may be eligible if they have no history of recurrent infections or malignancy. History of splenectomy.

[0605] Prior treatment with the following: (i) Cellular therapy (e.g., CAR T) or gene therapy product directed at any target. (ii) Receipt of an investigational therapy within 30 days or 5 drug-elimination half-lives (whichever is longer) prior to Day 1. (iii) Any anti-CD19 or anti-CD20 therapy such as blinatumomab, obinutuzumab, rituximab, ocrelizumab, or ofatumumab less than 3 months prior to Day 1. (iv) Non-biologic DMARD within 14 days prior to Day 1. These include but are not limited to: inhibitors of JAK, Bruton tyrosine kinase, or tyrosine kinase 2 (including baricitinib, tofacitinib, upadacitinib, filgotinib, ibrutinib, or fenebrutinib),

mycophenolic acid or derivatives, azathioprine, methotrexate, tacrolimus, cyclosporin, leflunomide. (v) Note: If on leflunomide cholestyramine administration is encouraged. (vii) Cyclophosphamide or a biologic immunomodulating therapy such as but not limited to belimumab, ustekinumab, anifrolumab, secukinumab, or abatacept during 1 month prior to Day 1. (viii) Active, clinically significant bacterial, viral, fungal, mycobacterial, parasitic, or other infection, including SARS-CoV-2 infection, within 14 days before Day 1.

[0606] Active or latent tuberculosis (TB) evidenced by a positive or indeterminant Interferon Gamma Release Assay (IGRA), unless the patient has documented previous completion of TB treatment and no current clinical indication of TB.

[0607] Previous or concurrent malignancy with the following exceptions: (i) Adequately treated basal cell or squamous cell carcinoma (adequate wound healing is required prior to Screening); (ii) In situ carcinoma of the cervix or breast, treated curatively and without evidence of recurrence for at least 3 years prior to Screening.

[0608] A primary malignancy which has been completely resected, or treated, and is in complete remission for at least 5 years prior to Screening.

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[0628] Additional embodiments of the disclosure are listed below:

[0629] 1. A method of treating an immune disorder characterized by B cell pathogenesis in a subject in need thereof, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising:

[0630] a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

[0631] HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and

[0632] b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

[0633] HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21.

[0634] 2. The method of embodiment 1, further comprising a third antigen-binding site that binds to human serum albumin comprising heavy chain complementarity determining regions (HCDR) wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 25 or 26, HCDR2 comprises the amino acid sequence of SEQ ID NO: 27, and HCDR3 comprises the amino acid sequence of SEQ ID NO: 28 or 29.

[0635] 3. A method of treating an immune disorder characterized by B cell pathogenesis in a subject in need thereof, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising:

[0636] a) a first antigen-binding site that binds to CD19 comprising a heavy chain variable domain (VH) comprising an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 1 and a light chain variable domain (VL) comprising an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 2; and

[0637] b) a second antigen-binding site that binds to human CD3 comprising a VH comprising an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 12 and a VL comprising an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 13.

[0638] 4. The method of embodiment 3, wherein the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to

CD19 comprises a VH comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 1; or alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 1.

[0639] 5. The method of embodiment 3, wherein the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to

CD19 comprises a VL comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 2; or alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO:2.

[0640] 6. The method of embodiment 3, wherein the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 12; or alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 12.

[0641] 7. The method of embodiment 3, wherein the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 13; or alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO:13.

[0642] 8. The method of embodiment 3, further comprising a third antigen-binding site that binds to human serum albumin (HSA) comprising a VH comprising an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 24.

[0643] 9. The method of embodiment 6, wherein the VH comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 24; or alternatively the VH comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 24.

[0644] 10. A method of treating an immune disorder characterized by B cell pathogenesis in a subject in need thereof, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 41.

[0645] 11. The method of embodiment 10, wherein the multi-specific binding protein comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid

sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 41; or alternatively the multi-specific binding protein comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 41.

[0646] 12. The method of any one of embodiments 1 to 9, wherein the first antigen-binding site comprises an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about

96% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 11; or alternatively the first antigen-binding site comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 11.

[0647] 13. The method of any one of embodiments 1 to 9, wherein the second antigen-binding site comprises an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 22 or 23; or alternatively the second antigen-binding site comprises

an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 22 or 23.

[0648] 14. The method of any one of embodiments 1 to 9, wherein the first antigen-binding site and/or the second antigen-binding site comprise a single-chain variable fragment (scFv).

[0649] 15. The method of embodiment 2 or embodiment 8, wherein the third antigen-binding site comprises a single-domain antibody (sdAb).

[0650] 16. The method of any one of embodiments 1 to 9, wherein the multi-specific binding protein comprises a single polypeptide chain.

[0651] 17. The method of any one of embodiments 1 to 9, wherein the multi-specific binding protein comprises a single polypeptide chain and the third antigen-binding site is positioned N-terminal to both the first antigen-binding site and the second antigen-binding site in the polypeptide chain;

[0652] or wherein the third antigen-binding site is positioned N-terminal to the first antigen-binding site, and the first antigen-binding site is positioned N-terminal to the second antigen-binding site in the polypeptide chain;

[0653] or wherein the third antigen-binding site is positioned N-terminal to the second antigen-binding site, and the second antigen-binding site is positioned N-terminal to the first antigen-binding site in the polypeptide chain.

[0654] 18. The method of any one of embodiments 1 to 9, wherein the multi-specific binding protein comprises a single polypeptide chain and the third antigen-binding site is positioned C-terminal to both the first antigen-binding site and the second antigen-binding site in the polypeptide chain;

[0655] or wherein the first antigen-binding site is positioned N-terminal to the second antigen-binding site, and the second antigen-binding site is positioned N-terminal to the third antigen-binding site in the polypeptide chain;

[0656] or wherein the second antigen-binding site is positioned N-terminal to the first antigen-binding site, and the first antigen-binding site is positioned N-terminal of the third antigen-binding site in the polypeptide chain.

[0657] 19. The method of any one of embodiments 1 to 9, wherein the multi-specific binding protein comprises a single polypeptide chain and the first antigen-binding site is

positioned N-terminal to the third antigen-binding site, and the third antigen-binding site is positioned N-terminal to the second antigen-binding site in the polypeptide chain;

[0658] or wherein the second antigen-binding site is positioned N-terminal to the third antigen-binding site, and the third antigen-binding site is positioned N-terminal binding protein the first antigen-binding site in the polypeptide chain.

[0659] 20. The method of any one of embodiments 1 to 11, wherein said immune disorder characterized by B cell pathogenesis is selected from the group consisting of SLE, rheumatoid arthritis, multiple sclerosis, type 1 diabetes, adult dermatomyositis, sine myositis, juvenile dermatomyositis, Sjögren's disease, neuromyelitis optica spectrum disorder, myasthenia gravis, ANCA-positive vasculitis, antiphospholipid syndrome, autoimmune cytopenias, autoimmune encephalitis, and pemphigus vulgaris.

[0660] 21. The method of any one of embodiments 1 to 11, wherein administration of said multi-specific binding protein produces B cell depletion in said subject within 96 hours of administration of said multi-specific binding protein.

[0661] 22. The method of any one of embodiments 1 to 11, wherein administration of said multi-specific binding protein produces a persistent B cell depletion that is sustained to at least 90 days after administration of said multi-specific binding protein.

[0662] 23. The method of any one of embodiments 1 to 11, wherein administration of said multi-specific binding protein produces a deep and/ or sustained B cell depletion in tissue.

[0663] 24. The method of embodiment 23, wherein the tissue is selected from the group consisting of bone marrow tissue, spleen tissue, axial lymph node tissue, and mandibular lymph node tissue.

[0664] 25. The method of any one of embodiments 1 to 11, wherein administration of said multi-specific binding protein produces at least about a 75% reduction in peripheral blood B cells.

[0665] 26. The method of any one of embodiments 1 to 11, wherein administration of said multi-specific binding protein produces at least about a 95% reduction in peripheral blood B cells.

[0666] 27. The method of any one of embodiments 1 to 11, wherein said subject is administered a dose of at least 10μg said multi-specific binding protein.

[0667] 28. The method of any one of embodiments 1 to 11, wherein said subject is administered a dose of at least 20μg said multi-specific binding protein.

[0668] 29. The method of any one of embodiments 1 to 11, wherein said subject is administered a dose of at least 30μg said multi-specific binding protein.

[0669] 30. The method of any one of embodiments 1 to 11, wherein said subject is administered a dose of at least 40μg said multi-specific binding protein.

[0670] 31. The method of any one of embodiments 1 to 11, wherein said subject is administered a dose of at least 50μg said multi-specific binding protein.

[0671] 32. The method of any one of embodiments 1 to 11, wherein said subject is administered a dose of at least 60μg said multi-specific binding protein.

[0672] 33. The method of any one of embodiments 1 to 11, wherein the subject is administered at least an initial dose and at least one target dose.

[0673] 34. The method of embodiment 33, wherein the target dose is at least about 2xs greater than the initial dose; alternative the target dose at least about 2.5xs greater than the initial dose; alternatively the target dose is at least about 3xs greater than the initial dose; alternatively the target dose is at least about 3.5xs greater than the initial dose; alternatively the target dose is at least about 4xs greater than the initial dose; alternatively the target dose is at least about 4.5xs greater than the initial dose; alternatively the target dose is at least about 5xs greater than the initial dose; alternatively the target dose is at least about 5.5xs greater than the initial dose; alternatively the target dose is at least about 6xs greater than the initial dose; alternatively the target dose is at least about 6.5xs greater than the initial dose; alternatively the target dose is at least about 7xs greater than the initial dose; alternatively the target dose is at least about 7.5xs greater than the initial dose; alternatively the target dose is at least about 8xs greater than the initial dose; alternatively the target dose is at least about 8.5xs greater than the initial dose; alternatively the target dose is at least about 9xs greater than the initial dose; alternatively the target dose is at least about 9.5xs greater than the initial dose; alternatively the target dose is at least about 10xs greater than the initial dose; or alternatively the target dose is at least about 10.5xs greater than the initial dose.

[0674]

[0675] 35. A method of achieving B cell depletion in a subject suffering from an autoimmune disease, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising:

[0676] a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

[0677] HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and

[0678] b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

[0679] HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21.

[0680] 36. The method of embodiment 35, further comprising a third antigen-binding site that binds to human serum albumin comprising heavy chain complementarity determining regions (HCDR) wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 25 or 26, HCDR2 comprises the amino acid sequence of SEQ ID NO: 27, and HCDR3 comprises the amino acid sequence of SEQ ID NO: 28 or 29.

[0681] 37. A method of achieving B cell depletion in a subject suffering from an autoimmune disease, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising:

[0682] a) a first antigen-binding site that binds to CD19 comprising a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 1 and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 2; and

[0683] b) a second antigen-binding site that binds to human CD3 comprising a VH comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 12 and a VL comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 13.

[0684] 38. The method of embodiment 37, wherein the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 1; or alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 1.

[0685] 39. The method of embodiment 37, wherein the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 2; or alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO:2.

[0686] 40. The method of embodiment 37, wherein the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 88% identical to

the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 12; or alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 12.

[0687] 41. The method of embodiment 37, wherein the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 91% identical to

the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 13; or alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO:13.

[0688]

[0689] 42. The method of embodiment 37, further comprising a third antigen-binding site that binds to human serum albumin (HSA) comprising a VH comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 24.

[0690] 43. The method of embodiment 42, wherein the VH comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least

about 93% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 24; or alternatively the VH comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 24.

[0691] 44. A method of achieving B cell depletion in a subject suffering from an autoimmune disease, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 41.

[0692] 45. The method of embodiment 44, wherein the multi-specific binding protein comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein

comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 41; or alternatively the multi-specific binding protein comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 41.

[0693] 46. The method of any one of embodiments 35 to 43, wherein the first antigen-binding site comprises an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 11; or alternatively the first antigen-binding site comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 11.

[0694] 47. The method of any one of embodiments 35 to 43, wherein the second antigen-binding site comprises an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 22 or 23; or alternatively the second antigen-binding site comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 22 or 23.

[0695] 48. The method of any one of embodiments 35 to 43, wherein the first antigen-binding site and/or the second antigen-binding site comprise a single-chain variable fragment (scFv).

[0696] 49. The method of embodiment 36 or embodiment 42, wherein the third antigen-binding site comprises a single-domain antibody (sdAb).

[0697] 50. The method of any one of embodiments 35 to 43, wherein the multi-specific binding protein comprises a single polypeptide chain.

[0698] 51. The method of any one of embodiments 35 to 43, wherein the multi-specific binding protein comprises a single polypeptide chain and the third antigen-binding site is positioned N-terminal to both the first antigen-binding site and the second antigen-binding site in the polypeptide chain;

[0699] or wherein the third antigen-binding site is positioned N-terminal to the first antigen-binding site, and the first antigen-binding site is positioned N-terminal to the second antigen-binding site in the polypeptide chain;

[0700] or wherein the third antigen-binding site is positioned N-terminal to the second antigen-binding site, and the second antigen-binding site is positioned N-terminal to the first antigen-binding site in the polypeptide chain.

[0701] 52. The method of any one of embodiments 35 to 43, wherein the multi-specific binding protein comprises a single polypeptide chain and the third antigen-binding site is positioned C-terminal to both the first antigen-binding site and the second antigen-binding site in the polypeptide chain;

[0702] or wherein the first antigen-binding site is positioned N-terminal to the second antigen-binding site, and the second antigen-binding site is positioned N-terminal to the third antigen-binding site in the polypeptide chain;

[0703] or wherein the second antigen-binding site is positioned N-terminal to the first antigen-binding site, and the first antigen-binding site is positioned N-terminal of the third antigen-binding site in the polypeptide chain.

[0704] 53. The method of any one of embodiments 35 to 43, wherein the multi-specific binding protein comprises a single polypeptide chain and the first antigen-binding site is positioned N-terminal to the third antigen-binding site, and the third antigen-binding site is positioned N-terminal to the second antigen-binding site in the polypeptide chain;

[0705] or wherein the second antigen-binding site is positioned N-terminal to the third antigen-binding site, and the third antigen-binding site is positioned N-terminal binding protein the first antigen-binding site in the polypeptide chain.

[0706] 54. The method of any one of embodiments 35 to 45, wherein said autoimmune disease is selected from the group consisting of SLE, rheumatoid arthritis, multiple sclerosis, type

1 diabetes, adult dermatomyositis, sine myositis, juvenile dermatomyositis, Sjögren's disease, neuromyelitis optica spectrum disorder, myasthenia gravis, ANCA-positive vasculitis, antiphospholipid syndrome, autoimmune cytopenias, autoimmune encephalitis, and pemphigus vulgaris.

[0707] 55. A method of treating SLE in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising:

[0708] a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

[0709] HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and

[0710] b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

[0711] HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21.

[0712] 56. The method of embodiment 55, further comprising a third antigen-binding site that binds to human serum albumin comprising heavy chain complementarity determining regions (HCDR) wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 25 or 26, HCDR2 comprises the amino acid sequence of SEQ ID NO: 27, and HCDR3 comprises the amino acid sequence of SEQ ID NO: 28 or 29.

[0713] 57. A method of treating SLE in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising:

[0714] a) a first antigen-binding site that binds to CD19 comprising a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to the amino

acid sequence of SEQ ID NO: 1 and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 2; and

[0715] b) a second antigen-binding site that binds to human CD3 comprising a VH comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 12 and a VL comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 13.

[0716] 58. The method of embodiment 57, wherein the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 1; or alternatively the first antigen-binding site that binds to

CD19 comprises a VH comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 1.

[0717] 59. The method of embodiment 57, wherein the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 2; or alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO:2.

[0718] 60. The method of embodiment 57, wherein the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 85% identical to

the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 12; or alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 12.

[0719] 61. The method of embodiment 57, wherein the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 90% identical to

the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 13; or alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO:13.

[0720] 62. The method of embodiment 57, further comprising a third antigen-binding site that binds to human serum albumin (HSA) comprising a VH comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 24.

[0721] 63. The method of embodiment 62, wherein the VH comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 92% identical to the amino

acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 24; or alternatively the VH comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 24.

[0722] 64. A method of treating SLE in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 41.

[0723] 65. The method of embodiment 64, wherein the multi-specific binding protein comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein

comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 41; or alternatively the multi-specific binding protein comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 41.

[0724] 66. The method of any one of embodiments 55 to 63, wherein the first antigen-binding site comprises an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 11; or alternatively the first antigen-binding site comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 11.

[0725] 67. The method of any one of embodiments 55 to 63, wherein the second antigen-binding site comprises an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 22 or 23; or alternatively the second antigen-binding site comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 22 or 23.

[0726] 68. The method of any one of embodiments 55 to 63, wherein the first antigen-binding site and/or the second antigen-binding site comprise a single-chain variable fragment (scFv).

[0727] 69. The method of embodiment 56 or embodiment 62, wherein the third antigen-binding site comprises a single-domain antibody (sdAb).

[0728] 70. The method of any one of embodiments 55 to 63, wherein the multi-specific binding protein comprises a single polypeptide chain.

[0729] 71. The method of any one of embodiments 55 to 63, wherein the multi-specific binding protein comprises a single polypeptide chain and the third antigen-binding site is positioned N-terminal to both the first antigen-binding site and the second antigen-binding site in the polypeptide chain;

[0730] or wherein the third antigen-binding site is positioned N-terminal to the first antigen-binding site, and the first antigen-binding site is positioned N-terminal to the second antigen-binding site in the polypeptide chain;

[0731] or wherein the third antigen-binding site is positioned N-terminal to the second antigen-binding site, and the second antigen-binding site is positioned N-terminal to the first antigen-binding site in the polypeptide chain.

[0732] 72. The method of any one of embodiments 55 to 63, wherein the multi-specific binding protein comprises a single polypeptide chain and the third antigen-binding site is positioned C-terminal to both the first antigen-binding site and the second antigen-binding site in the polypeptide chain;

[0733] or wherein the first antigen-binding site is positioned N-terminal to the second antigen-binding site, and the second antigen-binding site is positioned N-terminal to the third antigen-binding site in the polypeptide chain;

[0734] or wherein the second antigen-binding site is positioned N-terminal to the first antigen-binding site, and the first antigen-binding site is positioned N-terminal of the third antigen-binding site in the polypeptide chain.

[0735] 73. The method of any one of embodiments 55 to 63, wherein the multi-specific binding protein comprises a single polypeptide chain and the first antigen-binding site is positioned N-terminal to the third antigen-binding site, and the third antigen-binding site is positioned N-terminal to the second antigen-binding site in the polypeptide chain;

[0736] or wherein the second antigen-binding site is positioned N-terminal to the third antigen-binding site, and the third antigen-binding site is positioned N-terminal binding protein the first antigen-binding site in the polypeptide chain.

[0737] 74. The method of any one of embodiments 55 to 65, wherein said administration produces B cell depletion in said subject within 96 hours of administration of said multi-specific binding protein.

[0738] 75. The method of any one of embodiments 55 to 65, wherein said administration produces a persistent B-cell depletion that is sustained to at least 90 days after administration of said multi-specific binding protein.

[0739] 76. The method of any one of embodiments 55 to 65, wherein said subject is administered a dose of at least 10μg said multi-specific binding protein.

[0740] 77. The method of any one of embodiments 55 to 65, wherein said subject is administered a dose of at least 20μg said multi-specific binding protein.

[0741] 78. The method of any one of embodiments 55 to 65, wherein said subject is administered a dose of at least 30μg said multi-specific binding protein.

[0742] 79. The method of any one of embodiments 55 to 65, wherein said subject is administered a dose of at least 40μg said multi-specific binding protein.

[0743] 80. The method of any one of embodiments 55 to 65, wherein said subject is administered a dose of at least 50μg said multi-specific binding protein.

[0744] 81. The method of any one of embodiments 55 to 65, wherein said subject is administered a dose of at least 60μg said multi-specific binding protein.

[0745] 82. The method of any one of embodiments 55 to 65, wherein said subject has not received (i) Cellular therapy (CAR T) or gene therapy product directed at any target, (ii) Any anti-CD19 or anti-CD20 therapy, (iii) Inhibitors of JAK, Bruton tyrosine kinase, or tyrosine kinase 2, (iv) Tacrolimus, cyclosporin, voclosporin, azathioprine, or mycophenolic acid and its derivatives, or (v) Cyclophosphamide or a biologic therapy before administration of the multi-specific binding protein.

[0746] 83. A method of treating RA in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising:

[0747] a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

[0748] HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence

of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and

[0749] b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

[0750] HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21.

[0751] 84. The method of embodiment 83, further comprising a third antigen-binding site that binds to human serum albumin comprising heavy chain complementarity determining regions (HCDR) wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 25 or 26, HCDR2 comprises the amino acid sequence of SEQ ID NO: 27, and HCDR3 comprises the amino acid sequence of SEQ ID NO: 28 or 29.

[0752] 85. A method of treating RA in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising:

[0753] a) a first antigen-binding site that binds to CD19 comprising a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 1 and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 2; and

[0754] b) a second antigen-binding site that binds to human CD3 comprising a VH comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 12 and a VL comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 13.

[0755] 86. The method of embodiment 85, wherein the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to

CD19 comprises a VH comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 1; or alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 1.

[0756] 87. The method of embodiment 85, wherein the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to

CD19 comprises a VL comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 2; or alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO:2.

[0757] 88. The method of embodiment 85, wherein the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that

binds to CD3 comprises a VH comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 12; or alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 12.

[0758] 87. The method of embodiment 85, wherein the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that

binds to CD3 comprises a VL comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 13; or alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO:13.

[0759] 90. The method of embodiment 85, further comprising a third antigen-binding site that binds to human serum albumin (HSA) comprising a VH comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 24.

[0760] 91. The method of embodiment 88, wherein the VH comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 99% identical to the amino acid sequence of

SEQ ID NO: 24; or alternatively the VH comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 24.

[0761] 92. A method of treating RA in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 41.

[0762] 93. The method of embodiment 92, wherein the multi-specific binding protein comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 41; or alternatively the multi-specific binding protein comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 41.

[0763] 94. The method of any one of embodiments 83 to 91, wherein the first antigen-binding site comprises an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid

sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 11; or alternatively the first antigen-binding site comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 11.

[0764] 95. The method of any one of embodiments 83 to 91, wherein the second antigen-binding site comprises an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least

about 92% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 22 or 23; or alternatively the second antigen-binding site comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 22 or 23.

[0765] 96. The method of any one of embodiments 83 to 91, wherein the first antigen-binding site and/or the second antigen-binding site comprise a single-chain variable fragment (scFv).

[0766] 97. The method of embodiment 84 or embodiment 88, wherein the third antigen-binding site comprises a single-domain antibody (sdAb).

[0767] 98. The method of any one of embodiments 83 to 91, wherein the multi-specific binding protein comprises a single polypeptide chain.

[0768] 99. The method of embodiment 84 or embodiment 88, wherein the multi-specific binding protein comprises a single polypeptide chain and the third antigen-binding site is positioned N-terminal to both the first antigen-binding site and the second antigen-binding site in the polypeptide chain;

[0769] or wherein the third antigen-binding site is positioned N-terminal to the first antigen-binding site, and the first antigen-binding site is positioned N-terminal to the second antigen-binding site in the polypeptide chain;

[0770] or wherein the third antigen-binding site is positioned N-terminal to the second antigen-binding site, and the second antigen-binding site is positioned N-terminal to the first antigen-binding site in the polypeptide chain.

[0771] 100. The method of embodiment 84 or embodiment 88, wherein the multi-specific binding protein comprises a single polypeptide chain and the third antigen-binding site is positioned C-terminal to both the first antigen-binding site and the second antigen-binding site in the polypeptide chain;

[0772] or wherein the first antigen-binding site is positioned N-terminal to the second antigen-binding site, and the second antigen-binding site is positioned N-terminal to the third antigen-binding site in the polypeptide chain;

[0773] or wherein the second antigen-binding site is positioned N-terminal to the first antigen-binding site, and the first antigen-binding site is positioned N-terminal of the third antigen-binding site in the polypeptide chain.

[0774] 101. The method of embodiment 84 or embodiment 88, wherein the multi-specific binding protein comprises a single polypeptide chain and the first antigen-binding site is positioned N-terminal to the third antigen-binding site, and the third antigen-binding site is positioned N-terminal to the second antigen-binding site in the polypeptide chain;

[0775] or wherein the second antigen-binding site is positioned N-terminal to the third antigen-binding site, and the third antigen-binding site is positioned N-terminal binding protein the first antigen-binding site in the polypeptide chain.

[0776] 102. The method of any one of embodiments 83 to 93, wherein said administration produces B cell depletion in said subject within 96 hours of administration of said multi-specific binding protein.

[0777] 103. The method of any one of embodiments 83 to 93, wherein said administration produces a persistent B-cell depletion that is sustained to at least 90 days after administration of said multi-specific binding protein.

[0778] 104. The method of any one of embodiments 83 to 93, wherein said subject is administered a dose of at least 10μg said multi-specific binding protein.

[0779] 105. The method of any one of embodiments 83 to 93, wherein said subject is administered a dose of at least 20μg said multi-specific binding protein.

[0780] 106. The method of any one of embodiments 83 to 93, wherein said subject is administered a dose of at least 30μg said multi-specific binding protein.

[0781] 107. The method of any one of embodiments 83 to 93, wherein said subject is administered a dose of at least 40μg said multi-specific binding protein.

[0782] 108. The method of any one of embodiments 83 to 93, wherein said subject is administered a dose of at least 50μg said multi-specific binding protein.

[0783] 109. The method of any one of embodiments 83 to 93, wherein said subject is administered a dose of at least 60μg said multi-specific binding protein.

[0784] 110. The method of any one of embodiments 83 to 93, wherein said subject has not received (i) Cellular therapy (CAR T) or gene therapy product directed at any target, (ii) Any anti-CD19 or anti-CD20 therapy, (iii) Non-biologic DMARD or (iv) Cyclophosphamide or a biologic therapy before administration of the multi-specific binding protein.

[0785] 111. A method of treating Sjögren's disease in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising:

[0786] a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

[0787] HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and

[0788] b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

[0789] HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21.

[0790] 112. The method of embodiment 111, further comprising a third antigen-binding site that binds to human serum albumin comprising heavy chain complementarity determining regions (HCDR) wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 25 or 26, HCDR2 comprises the amino acid sequence of SEQ ID NO: 27, and HCDR3 comprises the amino acid sequence of SEQ ID NO: 28 or 29.

[0791] 113. A method of treating Sjögren's disease in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising:

[0792] a) a first antigen-binding site that binds to CD19 comprising a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 1 and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 2; and

[0793] b) a second antigen-binding site that binds to human CD3 comprising a VH comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 12 and a VL comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 13.

[0794] 114. The method of embodiment 113, wherein the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to

CD19 comprises a VH comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 1; or alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 1.

[0795] 115. The method of embodiment 113, wherein the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to

CD19 comprises a VL comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 2; or alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO:2.

[0796] 116. The method of embodiment 113, wherein the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that

binds to CD3 comprises a VH comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 12; or alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 12.

[0797] 117. The method of embodiment 113, wherein the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 13; or alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO:13.

[0798] 118. The method of embodiment 113, further comprising a third antigen-binding site that binds to human serum albumin (HSA) comprising a VH comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 24.

[0799] 119. The method of embodiment 118, wherein the VH comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 24; or alternatively the VH comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 24.

[0800] 120. A method of treating Sjögren's disease in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 41.

[0801] 121. The method of embodiment 120, wherein the multi-specific binding protein comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 90% identical

to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 41; or alternatively the multi-specific binding protein comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 41.

[0802] 122. The method of any one of embodiments 111 to 121, wherein the first antigen-binding site comprises an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 94%

identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 11; or alternatively the first antigen-binding site comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 11.

[0803] 123. The method of any one of embodiments 111 to 121, wherein the second antigen-binding site comprises an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least

about 98% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 22 or 23; or alternatively the second antigen-binding site comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 22 or 23.

[0804] 124. The method of any one of embodiments 111 to 121, wherein the first antigen-binding site and/or the second antigen-binding site comprise a single-chain variable fragment (scFv).

[0805] 125. The method of embodiment 112 or embodiment 118, wherein the third antigen-binding site comprises a single-domain antibody (sdAb).

[0806] 126. The method of any one of embodiments 111 to 121, wherein the multi-specific binding protein comprises a single polypeptide chain.

[0807] 127. The method of embodiment 112 or embodiment 118, wherein the multi-specific binding protein comprises a single polypeptide chain and the third antigen-binding site is positioned N-terminal to both the first antigen-binding site and the second antigen-binding site in the polypeptide chain;

[0808] or wherein the third antigen-binding site is positioned N-terminal to the first antigen-binding site, and the first antigen-binding site is positioned N-terminal to the second antigen-binding site in the polypeptide chain;

[0809] or wherein the third antigen-binding site is positioned N-terminal to the second antigen-binding site, and the second antigen-binding site is positioned N-terminal to the first antigen-binding site in the polypeptide chain.

[0810] 128. The method of embodiment 112 or embodiment 118, wherein the multi-specific binding protein comprises a single polypeptide chain and the third antigen-binding site is positioned C-terminal to both the first antigen-binding site and the second antigen-binding site in the polypeptide chain;

[0811] or wherein the first antigen-binding site is positioned N-terminal to the second antigen-binding site, and the second antigen-binding site is positioned N-terminal to the third antigen-binding site in the polypeptide chain;

[0812] or wherein the second antigen-binding site is positioned N-terminal to the first antigen-binding site, and the first antigen-binding site is positioned N-terminal of the third antigen-binding site in the polypeptide chain.

[0813] 129. The method of embodiment 112 or embodiment 118, wherein the multi-specific binding protein comprises a single polypeptide chain and the first antigen-binding site is positioned N-terminal to the third antigen-binding site, and the third antigen-binding site is positioned N-terminal to the second antigen-binding site in the polypeptide chain;

[0814] or wherein the second antigen-binding site is positioned N-terminal to the third antigen-binding site, and the third antigen-binding site is positioned N-terminal binding protein the first antigen-binding site in the polypeptide chain.

[0815] 130. The method of any one of embodiments 111 to 121, wherein said administration produces B cell depletion in said subject within 96 hours of administration of said multi-specific binding protein.

[0816] 131. The method of any one of embodiments 111 to 121, wherein said administration produces a persistent B-cell depletion that is sustained to at least 90 days after administration of said multi-specific binding protein.

[0817] 132. The method of any one of embodiments 111 to 121, wherein said subject is administered a dose of at least 10μg said multi-specific binding protein.

[0818] 133. The method of any one of embodiments 111 to 121, wherein said subject is administered a dose of at least 20μg said multi-specific binding protein.

[0819] 134. The method of any one of embodiments 111 to 121, wherein said subject is administered a dose of at least 30μg said multi-specific binding protein.

[0820] 135. The method of any one of embodiments 111 to 121, wherein said subject is administered a dose of at least 40μg said multi-specific binding protein.

[0821] 136. The method of any one of embodiments 111 to 121, wherein said subject is administered a dose of at least 50μg said multi-specific binding protein.

[0822] 137. The method of any one of embodiments 111 to 121, wherein said subject is administered a dose of at least 60μg said multi-specific binding protein.

[0823] 138. The method of any one of embodiments 111 to 121, wherein said subject has not received (i) Cellular therapy (CAR T) or gene therapy product directed at any target, (ii)

Any anti-CD19 or anti-CD20 therapy, (iii) Non-biologic DMARD or (iv) Cyclophosphamide or a biologic therapy before administration of the multi-specific binding protein.

[0824] 139. The method of any one of embodiments 111 to 121, wherein said subject has received leflunomide cholestyramine, glucocorticoids, antimalarials, or sialagogues prior to the administration of said multi-specific binding protein.

[0825] 140. The method of any one of embodiments 111 to 121, wherein after administration of said multi-specific binding protein, the subject has an achievement of disease response.

[0826] 141. The method of embodiment 140, wherein the achievement of disease response is a decrease in ESSDAI ≥ 3 (MCII), decrease in ESSPRI ≥ 1 or 15% (MCII), a ESSDAI < 5, or an ESSDAI equal to 0.

[0827] 142. A therapeutic composition comprising a polynucleotide encoding a multi-specific binding protein, wherein the polynucleotide comprises at least about 70% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42 or SEQ ID NO: 43.

[0828] 143. The therapeutic composition of embodiment 142, wherein the polynucleotide comprises at least about 80% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 85% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 88% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 90% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 91% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 92% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 93% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 94% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 95% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 96% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 97% nucleic acid sequence identity to the nucleic acid

sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 98% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 99% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; or alternatively the polynucleotide comprises at least about 100% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42.

[0829] 144. The therapeutic composition of embodiment 142, wherein the polynucleotide comprises at least about 80% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 85% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 88% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 90% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 91% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 92% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 93% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 94% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 95% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 96% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 97% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 98% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 99% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; or alternatively the polynucleotide comprises at least about 100% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43.

[0830] 145. The therapeutic composition of embodiment 142, wherein the polynucleotide encode a multi-specific binding protein, wherein the multi-specific binding protein comprises an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 41 or SEQ ID NO: 44.

[0831] 146. The therapeutic composition of embodiment 145, wherein the multi-specific binding protein comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 41; or alternatively the multi-specific binding protein comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 41.

[0832] 147. The therapeutic composition of embodiment 145, wherein the multi-specific binding protein comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein

comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 44; or alternatively the multi-specific binding protein comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 44.

[0833] 148. The therapeutic composition of any one of embodiments 142 to 147, wherein the polynucleotide is formulated and/or in communication with a delivery vehicle.

[0834] 149. The therapeutic composition of any one of embodiments 142 to 147, wherein the polynucleotide is at least partially encapsulated with a delivery vehicle.

[0835] 150. The therapeutic composition of embodiment 149, wherein the delivery vehicle is selected from the group consisting of amphipathic molecules, amino-lipidated peptides, tertiary amino lipidated cationic peptides, a cationic component, a peptoid, a lipoid, a liposome, a lipoplex, a lipid nanoparticle, a cationic lipid nanoparticle, a polymeric compound, and a conjugate.

[0836] 151. The therapeutic composition of any one of embodiments 142 to 147, wherein the therapeutic composition is configured to be administered subcutaneously.

[0837] 152. The therapeutic composition of any one of embodiments 142 to 147, wherein the composition is configured to be administered to a subject know to have or suspected to have an autoimmune disease.

[0838] 153. The therapeutic composition of embodiment 152, wherein the autoimmune disease is selected from the group consisting of SLE, rheumatoid arthritis, multiple sclerosis, type

1 diabetes, adult dermatomyositis, sine myositis, juvenile dermatomyositis, Sjögren's disease, neuromyelitis optica spectrum disorder, myasthenia gravis, ANCA-positive vasculitis, antiphospholipid syndrome, autoimmune cytopenias, autoimmune encephalitis, and pemphigus vulgaris.

[0839] 154. The therapeutic composition of any one of embodiments 142 to 147, further comprising one or more one or more therapeutically acceptable carriers, therapeutically acceptable diluents, therapeutically acceptable excipients or other therapeutic agents.

[0840] 155. The therapeutic composition of embodiment 154, wherein the therapeutically acceptable excipients are selected from the group consisting of salts, buffering agents, preservatives, antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes, emollients, emulsifiers, fillers, film formers, coatings, flavors, fragrances, glidants, lubricants, sorbents, suspending or dispersing agents, sweeteners, and waters of hydration.

[0841] 156. A method of treating an immune disorder characterized by B cell pathogenesis in a subject or a method of achieving B cell depletion in a subject suffering from an autoimmune disease, comprising administering a therapeutically effective amount of the therapeutic composition of any one of embodiments 142 to 155 to the subject.

[0842] 157. A method of treating SLE in a subject, comprising administering a therapeutically effective amount of the therapeutic composition of any one of embodiments 142 to 155 to the subject.

[0843] 158. A method of treating RA in a subject, comprising administering a therapeutically effective amount of the therapeutic composition of any one of embodiments 142 to 155 to the subject.

[0844] 159. A method of treating Sjögren's disease in a subject, comprising administering a therapeutically effective amount of the therapeutic composition of any one of embodiments 142 to 155 to the subject.

[0845] 160. A kit comprising the therapeutic composition of any one of embodiments 142 to 155 and instructions for use.

[0846] 161. The kit of embodiment 160, wherein the instructions for use include instructions for subcutaneous administration.

[0847] 162. The use of a multi-specific binding protein comprising:

[0848] a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

[0849] HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and

[0850] b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

[0851] HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21

[0852] in the manufacturer of a medicament for treating an immune disorder characterized by B cell pathogenesis in a subject or a method of achieving B cell depletion in a subject suffering from an autoimmune disease.

[0853] 163. The use of embodiment 162, wherein the immune disorder characterized by B cell pathogenesis or the autoimmune disease is selected from the group consisting of SLE, rheumatoid arthritis, multiple sclerosis, type 1 diabetes, adult dermatomyositis, sine myositis, juvenile dermatomyositis, Sjögren's disease, neuromyelitis optica spectrum disorder, myasthenia gravis, ANCA-positive vasculitis, antiphospholipid syndrome, autoimmune cytopenias, autoimmune encephalitis, and pemphigus vulgaris.

[0854] 164. The use of a multi-specific binding protein comprising:

[0855] a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

[0856] HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence

of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and

[0857] b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

[0858] HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21

[0859] in the manufacturer of a medicament for treating SLE in a subject in need thereof.

[0860] 165. The use of multi-specific binding protein comprising:

[0861] a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

[0862] HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and

[0863] b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

[0864] HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21

[0865] in the manufacturer of a medicament for treating RA in a subject in need thereof.

[0866] 166. The use of a multi-specific binding protein comprising:

[0867] a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

[0868] HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and

[0869] b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

[0870] HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21

[0871] in the manufacturer of a medicament for treating Sjögren's disease in a subject in need thereof.

[0872] 167. The use of any one of embodiments 162 to 166, wherein the multi-specific binding protein further comprises a third antigen-binding site that binds to human serum albumin comprising heavy chain complementarity determining regions (HCDR) wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 25 or 26, HCDR2 comprises the amino acid sequence of SEQ ID NO: 27, and HCDR3 comprises the amino acid sequence of SEQ ID NO: 28 or 29.

[0873] All features disclosed in the specification, including the claims, abstracts, drawings, and appendices, and all the steps in any method or process disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive. Each feature disclosed in the specification, including the claims, abstract, drawings,

and appendices can be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly stated otherwise, each feature disclosed is one example only of a generic series of equivalent or similar features.

[0874] It will be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

CLAIMS

1. A method of treating an immune disorder characterized by B cell pathogenesis in a subject in need thereof, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising:

a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and

b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21.

2. The method of claim 1, further comprising a third antigen-binding site that binds to human serum albumin comprising heavy chain complementarity determining regions (HCDR) wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 25 or 26, HCDR2 comprises the amino acid sequence of SEQ ID NO: 27, and HCDR3 comprises the amino acid sequence of SEQ ID NO: 28 or 29.

3. A method of treating an immune disorder characterized by B cell pathogenesis in a subject in need thereof, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising:

a) a first antigen-binding site that binds to CD19 comprising a heavy chain variable domain (VH) comprising an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 1 and a light chain variable domain (VL) comprising an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 2; and

b) a second antigen-binding site that binds to human CD3 comprising a VH comprising an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 12 and a VL comprising an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 13.

4. The method of claim 3, wherein the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 98% identical to the amino acid sequence of

SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 1; or alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 1.

5. The method of claim 3, wherein the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 2; or alternatively the first antigen-binding site that binds to CD19 comprises a VL

comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO:2.

6. The method of claim 3, wherein the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 12; or alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 12.

7. The method of claim 3, wherein the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 13; or alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO:13.

8. The method of claim 3, further comprising a third antigen-binding site that binds to human serum albumin (HSA) comprising a VH comprising an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 24.

9. The method of claim 6, wherein the VH comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 24; or alternatively the VH comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 24.

10. A method of treating an immune disorder characterized by B cell pathogenesis in a subject in need thereof, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 41.

11. The method of claim 10, wherein the multi-specific binding protein comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about

92% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 41; or alternatively the multi-specific binding protein comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 41.

12. The method of any one of claims 1 to 9, wherein the first antigen-binding site comprises an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid

sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 11; or alternatively the first antigen-binding site comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 11.

13. The method of any one of claims 1 to 9, wherein the second antigen-binding site comprises an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 22 or 23; or alternatively the second antigen-binding site comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 22 or 23.

14. The method of any one of claims 1 to 9, wherein the first antigen-binding site and/or the second antigen-binding site comprise a single-chain variable fragment (scFv).

15. The method of claim 2 or claim 8, wherein the third antigen-binding site comprises a single-domain antibody (sdAb).

16. The method of any one of claims 1 to 9, wherein the multi-specific binding protein comprises a single polypeptide chain.

17. The method of any one of claims 1 to 9, wherein the multi-specific binding protein comprises a single polypeptide chain and the third antigen-binding site is positioned N-terminal to both the first antigen-binding site and the second antigen-binding site in the polypeptide chain;

or wherein the third antigen-binding site is positioned N-terminal to the first antigen-binding site, and the first antigen-binding site is positioned N-terminal to the second antigen-binding site in the polypeptide chain;

or wherein the third antigen-binding site is positioned N-terminal to the second antigen-binding site, and the second antigen-binding site is positioned N-terminal to the first antigen-binding site in the polypeptide chain.

18. The method of any one of claims 1 to 9, wherein the multi-specific binding protein comprises a single polypeptide chain and the third antigen-binding site is positioned C-terminal to both the first antigen-binding site and the second antigen-binding site in the polypeptide chain;

or wherein the first antigen-binding site is positioned N-terminal to the second antigen-binding site, and the second antigen-binding site is positioned N-terminal to the third antigen-binding site in the polypeptide chain;

or wherein the second antigen-binding site is positioned N-terminal to the first antigen-binding site, and the first antigen-binding site is positioned N-terminal of the third antigen-binding site in the polypeptide chain.

19. The method of any one of claims 1 to 9, wherein the multi-specific binding protein comprises a single polypeptide chain and the first antigen-binding site is positioned N-terminal to the third antigen-binding site, and the third antigen-binding site is positioned N-terminal to the second antigen-binding site in the polypeptide chain;

or wherein the second antigen-binding site is positioned N-terminal to the third antigen-binding site, and the third antigen-binding site is positioned N-terminal binding protein the first antigen-binding site in the polypeptide chain.

20. The method of any one of claims 1 to 11, wherein said immune disorder characterized by B cell pathogenesis is selected from the group consisting of SLE, rheumatoid arthritis, multiple sclerosis, type 1 diabetes, adult dermatomyositis, sine myositis, juvenile dermatomyositis, Sjögren's disease, neuromyelitis optica spectrum disorder, myasthenia gravis, ANCA-positive vasculitis, antiphospholipid syndrome, autoimmune cytopenias, autoimmune encephalitis, and pemphigus vulgaris.

21. The method of any one of claims 1 to 11, wherein administration of said multi-specific binding protein produces B cell depletion in said subject within 96 hours of administration of said multi-specific binding protein.

22. The method of any one of claims 1 to 11, wherein administration of said multi-specific binding protein produces a persistent B cell depletion that is sustained to at least 90 days after administration of said multi-specific binding protein.

23. The method of any one of claims 1 to 11, wherein administration of said multi-specific binding protein produces a deep and/ or sustained B cell depletion in tissue.

24. The method of claim 23, wherein the tissue is selected from the group consisting of bone marrow tissue, spleen tissue, axial lymph node tissue, and mandibular lymph node tissue.

25. The method of any one of claims 1 to 11, wherein administration of said multi-specific binding protein produces at least about a 75% reduction in peripheral blood B cells.

26. The method of any one of claims 1 to 11, wherein administration of said multi-specific binding protein produces at least about a 95% reduction in peripheral blood B cells.

27. The method of any one of claims 1 to 11, wherein said subject is administered a dose of at least 10μg said multi-specific binding protein.

28. The method of any one of claims 1 to 11, wherein said subject is administered a dose of at least 20μg said multi-specific binding protein.

29. The method of any one of claims 1 to 11, wherein said subject is administered a dose of at least 30μg said multi-specific binding protein.

30. The method of any one of claims 1 to 11, wherein said subject is administered a dose of at least 40μg said multi-specific binding protein.

31. The method of any one of claims 1 to 11, wherein said subject is administered a dose of at least 50μg said multi-specific binding protein.

32. The method of any one of claims 1 to 11, wherein said subject is administered a dose of at least 60μg said multi-specific binding protein.

33. The method of any one of claims 1 to 11, wherein the subject is administered at least an initial dose and at least one target dose.

34. The method of claim 33, wherein the target dose is at least about 2xs greater than the initial dose; alternative the target dose at least about 2.5xs greater than the initial dose; alternatively the target dose is at least about 3xs greater than the initial dose; alternatively the target dose is at least about 3.5xs greater than the initial dose; alternatively the target dose is at least about 4xs greater than the initial dose; alternatively the target dose is at least about 4.5xs greater than the initial dose; alternatively the target dose is at least about 5xs greater than the initial dose; alternatively the target dose is at least about 5.5xs greater than the initial dose; alternatively the target dose is at least about 6xs greater than the initial dose; alternatively the target dose is at least about 6.5xs greater than the initial dose; alternatively the target dose is at least about 7xs greater than the initial dose; alternatively the target dose is at least about 7.5xs greater than the initial dose; alternatively the target dose is at least about 8xs greater than the initial dose; alternatively the target dose is at least about 8.5xs greater than the initial dose; alternatively the target dose is at least about 9xs greater than the initial dose; alternatively the target dose is at least about 9.5xs greater than the initial dose; alternatively the target dose is at least about 10xs greater than the initial dose; or alternatively the target dose is at least about 10.5xs greater than the initial dose.

35. A method of achieving B cell depletion in a subject suffering from an autoimmune disease, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising:

a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and

b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21.

36. The method of claim 35, further comprising a third antigen-binding site that binds to human serum albumin comprising heavy chain complementarity determining regions (HCDR) wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 25 or 26, HCDR2 comprises the amino acid sequence of SEQ ID NO: 27, and HCDR3 comprises the amino acid sequence of SEQ ID NO: 28 or 29.

37. A method of achieving B cell depletion in a subject suffering from an autoimmune disease, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising:

a) a first antigen-binding site that binds to CD19 comprising a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 1 and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 2; and

b) a second antigen-binding site that binds to human CD3 comprising a VH comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 12 and a VL comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 13.

38. The method of claim 37, wherein the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 98% identical to the amino acid

sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 1; or alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 1.

39. The method of claim 37, wherein the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 2; or alternatively the first antigen-binding site that binds to CD19

comprises a VL comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO:2.

40. The method of claim 37, wherein the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 12; or alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 12.

41. The method of claim 37, wherein the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 13; or alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO:13.

42. The method of claim 37, further comprising a third antigen-binding site that binds to human serum albumin (HSA) comprising a VH comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 24.

43. The method of claim 42, wherein the VH comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 24; or alternatively the VH comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 24.

44. A method of achieving B cell depletion in a subject suffering from an autoimmune disease, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 41.

45. The method of claim 44, wherein the multi-specific binding protein comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 90% identical to the amino acid

sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 41; or alternatively the multi-specific binding protein comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 41.

46. The method of any one of claims 35 to 43, wherein the first antigen-binding site comprises an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least

about 95% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 11; or alternatively the first antigen-binding site comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 11.

47. The method of any one of claims 35 to 43, wherein the second antigen-binding site comprises an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ

ID NO: 22 or 23; or alternatively the second antigen-binding site comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 22 or 23.

48. The method of any one of claims 35 to 43, wherein the first antigen-binding site and/or the second antigen-binding site comprise a single-chain variable fragment (scFv).

49. The method of claim 36 or claim 42, wherein the third antigen-binding site comprises a single-domain antibody (sdAb).

50. The method of any one of claims 35 to 43, wherein the multi-specific binding protein comprises a single polypeptide chain.

51. The method of any one of claims 35 to 43, wherein the multi-specific binding protein comprises a single polypeptide chain and the third antigen-binding site is positioned N-terminal to both the first antigen-binding site and the second antigen-binding site in the polypeptide chain;

or wherein the third antigen-binding site is positioned N-terminal to the first antigen-binding site, and the first antigen-binding site is positioned N-terminal to the second antigen-binding site in the polypeptide chain;

or wherein the third antigen-binding site is positioned N-terminal to the second antigen-binding site, and the second antigen-binding site is positioned N-terminal to the first antigen-binding site in the polypeptide chain.

52. The method of any one of claims 35 to 43, wherein the multi-specific binding protein comprises a single polypeptide chain and the third antigen-binding site is positioned C-terminal to both the first antigen-binding site and the second antigen-binding site in the polypeptide chain;

or wherein the first antigen-binding site is positioned N-terminal to the second antigen-binding site, and the second antigen-binding site is positioned N-terminal to the third antigen-binding site in the polypeptide chain;

or wherein the second antigen-binding site is positioned N-terminal to the first antigen-binding site, and the first antigen-binding site is positioned N-terminal of the third antigen-binding site in the polypeptide chain.

53. The method of any one of claims 35 to 43, wherein the multi-specific binding protein comprises a single polypeptide chain and the first antigen-binding site is positioned N-terminal to the third antigen-binding site, and the third antigen-binding site is positioned N-terminal to the second antigen-binding site in the polypeptide chain;

or wherein the second antigen-binding site is positioned N-terminal to the third antigen-binding site, and the third antigen-binding site is positioned N-terminal binding protein the first antigen-binding site in the polypeptide chain.

54. The method of any one of claims 35 to 45, wherein said autoimmune disease is selected from the group consisting of SLE, rheumatoid arthritis, multiple sclerosis, type 1 diabetes, adult dermatomyositis, sine myositis, juvenile dermatomyositis, Sjögren's disease, neuromyelitis optica spectrum disorder, myasthenia gravis, ANCA-positive vasculitis, antiphospholipid syndrome, autoimmune cytopenias, autoimmune encephalitis, and pemphigus vulgaris.

55. A method of treating SLE in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising:

a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and

b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2

comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21.

56. The method of claim 55, further comprising a third antigen-binding site that binds to human serum albumin comprising heavy chain complementarity determining regions (HCDR) wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 25 or 26, HCDR2 comprises the amino acid sequence of SEQ ID NO: 27, and HCDR3 comprises the amino acid sequence of SEQ ID NO: 28 or 29.

57. A method of treating SLE in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising:

a) a first antigen-binding site that binds to CD19 comprising a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 1 and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 2; and

b) a second antigen-binding site that binds to human CD3 comprising a VH comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 12 and a VL comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 13.

58. The method of claim 57, wherein the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 93% identical to the amino acid

sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 1; or alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 1.

59. The method of claim 57, wherein the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 95% identical to the amino acid

sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 2; or alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO:2.

60. The method of claim 57, wherein the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 97% identical to the amino acid

sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 12; or alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 12.

61. The method of claim 57, wherein the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 99% identical to the amino acid

sequence of SEQ ID NO: 13; or alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO:13.

62. The method of claim 57, further comprising a third antigen-binding site that binds to human serum albumin (HSA) comprising a VH comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 24.

63. The method of claim 62, wherein the VH comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 24; or alternatively the VH comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 24.

64. A method of treating SLE in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 41.

65. The method of claim 64, wherein the multi-specific binding protein comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about

88% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 41; or alternatively the multi-specific binding protein comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 41.

66. The method of any one of claims 55 to 63, wherein the first antigen-binding site comprises an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site

comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 11; or alternatively the first antigen-binding site comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 11.

67. The method of any one of claims 55 to 63, wherein the second antigen-binding site comprises an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 98% identical to the

amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 22 or 23; or alternatively the second antigen-binding site comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 22 or 23.

68. The method of any one of claims 55 to 63, wherein the first antigen-binding site and/or the second antigen-binding site comprise a single-chain variable fragment (scFv).

69. The method of claim 56 or claim 62, wherein the third antigen-binding site comprises a single-domain antibody (sdAb).

70. The method of any one of claims 55 to 63, wherein the multi-specific binding protein comprises a single polypeptide chain.

71. The method of any one of claims 55 to 63, wherein the multi-specific binding protein comprises a single polypeptide chain and the third antigen-binding site is positioned N-terminal to both the first antigen-binding site and the second antigen-binding site in the polypeptide chain;

or wherein the third antigen-binding site is positioned N-terminal to the first antigen-binding site, and the first antigen-binding site is positioned N-terminal to the second antigen-binding site in the polypeptide chain;

or wherein the third antigen-binding site is positioned N-terminal to the second antigen-binding site, and the second antigen-binding site is positioned N-terminal to the first antigen-binding site in the polypeptide chain.

72. The method of any one of claims 55 to 63, wherein the multi-specific binding protein comprises a single polypeptide chain and the third antigen-binding site is positioned C-terminal to both the first antigen-binding site and the second antigen-binding site in the polypeptide chain;

or wherein the first antigen-binding site is positioned N-terminal to the second antigen-binding site, and the second antigen-binding site is positioned N-terminal to the third antigen-binding site in the polypeptide chain;

or wherein the second antigen-binding site is positioned N-terminal to the first antigen-binding site, and the first antigen-binding site is positioned N-terminal of the third antigen-binding site in the polypeptide chain.

73. The method of any one of claims 55 to 63, wherein the multi-specific binding protein comprises a single polypeptide chain and the first antigen-binding site is positioned N-terminal to the third antigen-binding site, and the third antigen-binding site is positioned N-terminal to the second antigen-binding site in the polypeptide chain;

or wherein the second antigen-binding site is positioned N-terminal to the third antigen-binding site, and the third antigen-binding site is positioned N-terminal binding protein the first antigen-binding site in the polypeptide chain.

74. The method of any one of claims 55 to 65, wherein said administration produces B cell depletion in said subject within 96 hours of administration of said multi-specific binding protein.

75. The method of any one of claims 55 to 65, wherein said administration produces a persistent B-cell depletion that is sustained to at least 90 days after administration of said multi-specific binding protein.

76. The method of any one of claims 55 to 65, wherein said subject is administered a dose of at least 10μg said multi-specific binding protein.

77. The method of any one of claims 55 to 65, wherein said subject is administered a dose of at least 20μg said multi-specific binding protein.

78. The method of any one of claims 55 to 65, wherein said subject is administered a dose of at least 30μg said multi-specific binding protein.

79. The method of any one of claims 55 to 65, wherein said subject is administered a dose of at least 40μg said multi-specific binding protein.

80. The method of any one of claims 55 to 65, wherein said subject is administered a dose of at least 50μg said multi-specific binding protein.

81. The method of any one of claims 55 to 65, wherein said subject is administered a dose of at least 60μg said multi-specific binding protein.

82. The method of any one of claims 55 to 65, wherein said subject has not received (i) Cellular therapy (CAR T) or gene therapy product directed at any target, (ii) Any anti-CD19 or anti-CD20 therapy, (iii) Inhibitors of JAK, Bruton tyrosine kinase, or tyrosine kinase 2, (iv) Tacrolimus,

cyclosporin, voclosporin, azathioprine, or mycophenolic acid and its derivatives, or (v) Cyclophosphamide or a biologic therapy prior to the administration of the multi-specific binding protein.

83. A method of treating RA in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising:

a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and

b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21.

84. The method of claim 83, further comprising a third antigen-binding site that binds to human serum albumin comprising heavy chain complementarity determining regions (HCDR) wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 25 or 26, HCDR2 comprises the amino acid sequence of SEQ ID NO: 27, and HCDR3 comprises the amino acid sequence of SEQ ID NO: 28 or 29.

85. A method of treating RA in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising:

a) a first antigen-binding site that binds to CD19 comprising a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 1 and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 2; and

b) a second antigen-binding site that binds to human CD3 comprising a VH comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 12 and a VL comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 13.

86. The method of claim 85, wherein the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 98% identical to the amino acid

sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 1; or alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 1.

87. The method of claim 85, wherein the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 2; or alternatively the first antigen-binding site that binds to CD19

comprises a VL comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO:2.

88. The method of claim 85, wherein the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 12; or alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 12.

89. The method of claim 85, wherein the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 13; or alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO:13.

90. The method of claim 85, further comprising a third antigen-binding site that binds to human serum albumin (HSA) comprising a VH comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 24.

91. The method of claim 88, wherein the VH comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 24; or alternatively the VH comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 24.

92. A method of treating RA in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 41.

93. The method of claim 92, wherein the multi-specific binding protein comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific

binding protein comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 41; or alternatively the multi-specific binding protein comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 41.

94. The method of any one of claims 83 to 91, wherein the first antigen-binding site comprises an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 11; alternatively

the first antigen-binding site comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 11; or alternatively the first antigen-binding site comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 11.

95. The method of any one of claims 83 to 91, wherein the second antigen-binding site comprises an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 22 or 23; or alternatively the second antigen-binding site comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 22 or 23.

96. The method of any one of claims 83 to 91, wherein the first antigen-binding site and/or the second antigen-binding site comprise a single-chain variable fragment (scFv).

97. The method of claim 84 or claim 88, wherein the third antigen-binding site comprises a single-domain antibody (sdAb).

98. The method of any one of claims 83 to 91, wherein the multi-specific binding protein comprises a single polypeptide chain.

99. The method of claim 84 or claim 88, wherein the multi-specific binding protein comprises a single polypeptide chain and the third antigen-binding site is positioned N-terminal to both the first antigen-binding site and the second antigen-binding site in the polypeptide chain;

or wherein the third antigen-binding site is positioned N-terminal to the first antigen-binding site, and the first antigen-binding site is positioned N-terminal to the second antigen-binding site in the polypeptide chain;

or wherein the third antigen-binding site is positioned N-terminal to the second antigen-binding site, and the second antigen-binding site is positioned N-terminal to the first antigen-binding site in the polypeptide chain.

100. The method of claim 84 or claim 88, wherein the multi-specific binding protein comprises a single polypeptide chain and the third antigen-binding site is positioned C-terminal to both the first antigen-binding site and the second antigen-binding site in the polypeptide chain;

or wherein the first antigen-binding site is positioned N-terminal to the second antigen-binding site, and the second antigen-binding site is positioned N-terminal to the third antigen-binding site in the polypeptide chain;

or wherein the second antigen-binding site is positioned N-terminal to the first antigen-binding site, and the first antigen-binding site is positioned N-terminal of the third antigen-binding site in the polypeptide chain.

101. The method of claim 84 or claim 88, wherein the multi-specific binding protein comprises a single polypeptide chain and the first antigen-binding site is positioned N-terminal to the third antigen-binding site, and the third antigen-binding site is positioned N-terminal to the second antigen-binding site in the polypeptide chain;

or wherein the second antigen-binding site is positioned N-terminal to the third antigen-binding site, and the third antigen-binding site is positioned N-terminal binding protein the first antigen-binding site in the polypeptide chain.

102. The method of any one of claims 83 to 93, wherein said administration produces B cell depletion in said subject within 96 hours of administration of said multi-specific binding protein.

103. The method of any one of claims 83 to 93, wherein said administration produces a persistent B-cell depletion that is sustained to at least 90 days after administration of said multi-specific binding protein.

104. The method of any one of claims 83 to 93, wherein said subject is administered a dose of at least 10μg said multi-specific binding protein.

105. The method of any one of claims 83 to 93, wherein said subject is administered a dose of at least 20μg said multi-specific binding protein.

106. The method of any one of claims 83 to 93, wherein said subject is administered a dose of at least 30μg said multi-specific binding protein.

107. The method of any one of claims 83 to 93, wherein said subject is administered a dose of at least 40μg said multi-specific binding protein.

108. The method of any one of claims 83 to 93, wherein said subject is administered a dose of at least 50μg said multi-specific binding protein.

109. The method of any one of claims 83 to 93, wherein said subject is administered a dose of at least 60μg said multi-specific binding protein.

110. The method of any one of claims 83 to 93, wherein said subject has not received (i) Cellular therapy (CAR T) or gene therapy product directed at any target, (ii) Any anti-CD19 or anti-CD20 therapy, (iii) Non-biologic DMARD or (iv) Cyclophosphamide or a biologic therapy prior to the administration of the multi-specific binding protein.

111. A method of treating Sjögren's disease in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising:

a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and

b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21.

112. The method of claim 111, further comprising a third antigen-binding site that binds to human serum albumin comprising heavy chain complementarity determining regions (HCDR) wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 25 or 26, HCDR2 comprises the amino acid sequence of SEQ ID NO: 27, and HCDR3 comprises the amino acid sequence of SEQ ID NO: 28 or 29.

113. A method of treating Sjögren's disease in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising:

a) a first antigen-binding site that binds to CD19 comprising a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 1 and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 2; and

b) a second antigen-binding site that binds to human CD3 comprising a VH comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 12 and a VL comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 13.

114. The method of claim 113, wherein the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 1; alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 1; or alternatively the first antigen-binding site that binds to CD19 comprises a VH comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 1.

115. The method of claim 113, wherein the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 2; alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 2; or alternatively the first antigen-binding site that binds to CD19 comprises a VL comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO:2.

116. The method of claim 113, wherein the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 88% identical to the amino acid

sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 12; alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 12; or alternatively the second antigen-binding site that binds to CD3 comprises a VH comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 12.

117. The method of claim 113, wherein the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 91% identical to the amino acid

sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 13; alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 13; or alternatively the second antigen-binding site that binds to CD3 comprises a VL comprising an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO:13.

118. The method of claim 113, further comprising a third antigen-binding site that binds to human serum albumin (HSA) comprising a VH comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 24.

119. The method of claim 118, wherein the VH comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 93% identical to the

amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 24; alternatively the VH comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 24; or alternatively the VH comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 24.

120. A method of treating Sjögren's disease in a subject, wherein said method comprises subcutaneously administering to the subject a multi-specific binding protein comprising an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 41.

121. The method of claim 120, wherein the multi-specific binding protein comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 41;

alternatively the multi-specific binding protein comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 41; or alternatively the multi-specific binding protein comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 41.

122. The method of any one of claims 111 to 121, wherein the first antigen-binding site comprises an amino acid sequence at least about 80% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 11; alternatively the first antigen-binding site comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 11; or alternatively the first antigen-binding site comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 11.

123. The method of any one of claims 111 to 121, wherein the second antigen-binding site comprises an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID

NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 22 or 23; alternatively the second antigen-binding site comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 22 or 23; or alternatively the second antigen-binding site comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 22 or 23.

124. The method of any one of claims 111 to 121, wherein the first antigen-binding site and/or the second antigen-binding site comprise a single-chain variable fragment (scFv).

125. The method of claim 112 or claim 118, wherein the third antigen-binding site comprises a single-domain antibody (sdAb).

126. The method of any one of claims 111 to 121, wherein the multi-specific binding protein comprises a single polypeptide chain.

127. The method of claim 112 or claim 118, wherein the multi-specific binding protein comprises a single polypeptide chain and the third antigen-binding site is positioned N-terminal to both the first antigen-binding site and the second antigen-binding site in the polypeptide chain;

or wherein the third antigen-binding site is positioned N-terminal to the first antigen-binding site, and the first antigen-binding site is positioned N-terminal to the second antigen-binding site in the polypeptide chain;

or wherein the third antigen-binding site is positioned N-terminal to the second antigen-binding site, and the second antigen-binding site is positioned N-terminal to the first antigen-binding site in the polypeptide chain.

128. The method of claim 112 or claim 118, wherein the multi-specific binding protein comprises a single polypeptide chain and the third antigen-binding site is positioned C-terminal to both the first antigen-binding site and the second antigen-binding site in the polypeptide chain;

or wherein the first antigen-binding site is positioned N-terminal to the second antigen-binding site, and the second antigen-binding site is positioned N-terminal to the third antigen-binding site in the polypeptide chain;

or wherein the second antigen-binding site is positioned N-terminal to the first antigen-binding site, and the first antigen-binding site is positioned N-terminal of the third antigen-binding site in the polypeptide chain.

129. The method of claim 112 or claim 118, wherein the multi-specific binding protein comprises a single polypeptide chain and the first antigen-binding site is positioned N-terminal to the third antigen-binding site, and the third antigen-binding site is positioned N-terminal to the second antigen-binding site in the polypeptide chain;

or wherein the second antigen-binding site is positioned N-terminal to the third antigen-binding site, and the third antigen-binding site is positioned N-terminal binding protein the first antigen-binding site in the polypeptide chain.

130. The method of any one of claims 111 to 121, wherein said administration produces B cell depletion in said subject within 96 hours of administration of said multi-specific binding protein.

131. The method of any one of claims 111 to 121, wherein said administration produces a persistent B-cell depletion that is sustained to at least 90 days after administration of said multi-specific binding protein.

132. The method of any one of claims 111 to 121, wherein said subject is administered a dose of at least 10μg said multi-specific binding protein.

133. The method of any one of claims 111 to 121, wherein said subject is administered a dose of at least 20μg said multi-specific binding protein.

134. The method of any one of claims 111 to 121, wherein said subject is administered a dose of at least 30μg said multi-specific binding protein.

135. The method of any one of claims 111 to 121, wherein said subject is administered a dose of at least 40μg said multi-specific binding protein.

136. The method of any one of claims 111 to 121, wherein said subject is administered a dose of at least 50μg said multi-specific binding protein.

137. The method of any one of claims 111 to 121, wherein said subject is administered a dose of at least 60μg said multi-specific binding protein.

138. The method of any one of claims 111 to 121, wherein said subject has not received (i) Cellular therapy (CAR T) or gene therapy product directed at any target, (ii) Any anti-CD19 or anti-CD20 therapy, (iii) Non-biologic DMARD or (iv) Cyclophosphamide or a biologic therapy prior to the administration of the multi-specific binding protein.

139. The method of any one of claims 111 to 121, wherein said subject has received leflunomide cholestyramine, glucocorticoids, antimalarials, or sialagogues prior to the administration of said multi-specific binding protein.

140. The method of any one of claims 111 to 121, wherein after administration of said multi-specific binding protein, the subject has an achievement of disease response.

141. The method of claim 140, wherein the achievement of disease response is a decrease in ESSDAI $\geq$ 3 (MCII), decrease in ESSPRI $\geq$ 1 or 15% (MCII), a ESSDAI < 5, or an ESSDAI equal to 0.

142. A therapeutic composition comprising a polynucleotide encoding a multi-specific binding protein, wherein the polynucleotide comprises at least about 70% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42 or SEQ ID NO: 43.

143. The therapeutic composition of claim 142, wherein the polynucleotide comprises at least about 80% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 85% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 88% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 90% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 91% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 92% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 93% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 94% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 95% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 96% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 97% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 98% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; alternatively the polynucleotide comprises at least about 99% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42; or alternatively the polynucleotide comprises at least about 100% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 42.

144. The therapeutic composition of claim 142, wherein the polynucleotide comprises at least about 80% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 85% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 88% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively

the polynucleotide comprises at least about 90% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 91% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 92% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 93% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 94% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 95% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 96% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 97% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 98% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; alternatively the polynucleotide comprises at least about 99% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43; or alternatively the polynucleotide comprises at least about 100% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 43.

145. The therapeutic composition of claim 142, wherein the polynucleotide encode a multi-specific binding protein, wherein the multi-specific binding protein comprises an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 41 or SEQ ID NO: 44.

146. The therapeutic composition of claim 145, wherein the multi-specific binding protein comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 93% identical to the amino acid

sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 41; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 41; or alternatively the multi-specific binding protein comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 41.

147. The therapeutic composition of claim 145, wherein the multi-specific binding protein comprises an amino acid sequence at least about 85% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 88% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 90% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 91% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 92% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 93% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 94% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 95% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 96% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 97% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific binding protein comprises an amino acid sequence at least about 98% identical to the amino acid sequence of SEQ ID NO: 44; alternatively the multi-specific

binding protein comprises an amino acid sequence at least about 99% identical to the amino acid sequence of SEQ ID NO: 44; or alternatively the multi-specific binding protein comprises an amino acid sequence at least about 100% identical to the amino acid sequence of SEQ ID NO: 44.

148. The therapeutic composition of any one of claims 142 to 147, wherein the polynucleotide is formulated and/or in communication with a delivery vehicle.

149. The therapeutic composition of any one of claims 142 to 147, wherein the polynucleotide is at least partially encapsulated with a delivery vehicle.

150. The therapeutic composition of claim 149, wherein the delivery vehicle is selected from the group consisting of amphipathic molecules, amino-lipidated peptides, tertiary amino lipidated cationic peptides, a cationic component, a peptoid, a lipoid, a liposome, a lipoplex, a lipid nanoparticle, a cationic lipid nanoparticle, a polymeric compound, and a conjugate.

151. The therapeutic composition of any one of claims 142 to 147, wherein the therapeutic composition is configured to be administered subcutaneously.

152. The therapeutic composition of any one of claims 142 to 147, wherein the composition is configured to be administered to a subject know to have or suspected to have an autoimmune disease.

153. The therapeutic composition of claim 152, wherein the autoimmune disease is selected from the group consisting of SLE, rheumatoid arthritis, multiple sclerosis, type 1 diabetes, adult dermatomyositis, sine myositis, juvenile dermatomyositis, Sjögren's disease, neuromyelitis optica spectrum disorder, myasthenia gravis, ANCA-positive vasculitis, antiphospholipid syndrome, autoimmune cytopenias, autoimmune encephalitis, and pemphigus vulgaris.

154. The therapeutic composition of any one of claims 142 to 147, further comprising one or more one or more therapeutically acceptable carriers, therapeutically acceptable diluents, therapeutically acceptable excipients or other therapeutic agents.

155. The therapeutic composition of claim 154, wherein the therapeutically acceptable excipients are selected from the group consisting of salts, buffering agents, preservatives, antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes, emollients,

emulsifiers, fillers, film formers, coatings, flavors, fragrances, glidants, lubricants, sorbents, suspending or dispersing agents, sweeteners, and waters of hydration.

156. A method of treating an immune disorder characterized by B cell pathogenesis in a subject or a method of achieving B cell depletion in a subject suffering from an autoimmune disease, comprising administering a therapeutically effective amount of the therapeutic composition of any one of claims 142 to 155 to the subject.

157. A method of treating SLE in a subject, comprising administering a therapeutically effective amount of the therapeutic composition of any one of claims 142 to 155 to the subject.

158. A method of treating RA in a subject, comprising administering a therapeutically effective amount of the therapeutic composition of any one of claims 142 to 155 to the subject.

159. A method of treating Sjögren's disease in a subject, comprising administering a therapeutically effective amount of the therapeutic composition of any one of claims 142 to 155 to the subject.

160. A kit comprising the therapeutic composition of any one of claims 142 to 155 and instructions for use.

161. The kit of claim 160, wherein the instructions for use include instructions for subcutaneous administration.

162. The use of a multi-specific binding protein comprising:

a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and

b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21

in the manufacturer of a medicament for treating an immune disorder characterized by B cell pathogenesis in a subject or a method of achieving B cell depletion in a subject suffering from an autoimmune disease.

163. The use of claim 162, wherein the immune disorder characterized by B cell pathogenesis or the autoimmune disease is selected from the group consisting of SLE, rheumatoid arthritis, multiple sclerosis, type 1 diabetes, adult dermatomyositis, sine myositis, juvenile dermatomyositis, Sjögren's disease, neuromyelitis optica spectrum disorder, myasthenia gravis, ANCA-positive vasculitis, antiphospholipid syndrome, autoimmune cytopenias, autoimmune encephalitis, and pemphigus vulgaris.

164. The use of a multi-specific binding protein comprising:

a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and

b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21

in the manufacturer of a medicament for treating SLE in a subject in need thereof.

165. The use of multi-specific binding protein comprising:

a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and

b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21

in the manufacturer of a medicament for treating RA in a subject in need thereof.

166. The use of a multi-specific binding protein comprising:

a) a first antigen-binding site that to binds human CD19, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

HCDR1 comprises the amino acid sequence of SEQ ID NO: 3 or 4, HCDR2 comprises the amino acid sequence of SEQ ID NO: 5, HCDR3 comprises the amino acid sequence of SEQ ID NO: 6 or 7, LCDR1 comprises the amino acid sequence of SEQ ID NO: 8, LCDR2 comprises the amino acid sequence of SEQ ID NO: 9, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 10; and

b) a second antigen-binding domain that binds to CD3, comprising heavy chain complementarity determining regions (HCDR) and light chain complementarity determining regions (LCDR), wherein:

HCDR1 comprises the amino acid sequence of SEQ ID NO: 14 or 15, HCDR2 comprises the amino acid sequence of SEQ ID NO: 16, HCDR3 comprises the amino acid sequence of SEQ ID NO: 17 or 18, LCDR1 comprises the amino acid sequence of SEQ ID NO: 19, LCDR2 comprises the amino acid sequence of SEQ ID NO: 20, and LCDR3 comprises the amino acid sequence of SEQ ID NO: 21

in the manufacturer of a medicament for treating Sjögren's disease in a subject in need thereof.

167. The use of any one of claims 162 to 166, wherein the multi-specific binding protein further comprises a third antigen-binding site that binds to human serum albumin comprising heavy chain complementarity determining regions (HCDR) wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 25 or 26, HCDR2 comprises the amino acid sequence of SEQ ID NO: 27, and HCDR3 comprises the amino acid sequence of SEQ ID NO: 28 or 29.