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(54) **Titre : PROCEDES DE REDUCTION DE LA PRODUCTION D'IMMUNOGLOBULINES IGA, IGM ET/OU IGG A L'AIDE DE VARIANTS DE SBCMA ET LEURS PROTEINES DE FUSION FC**
(54) **Title: METHODS OF REDUCING PRODUCTION OF IgA, IgM AND/OR IgG USING sBCMA VARIANTS AND FC FUSION PROTEINS THEREOF**

(57) **Abrégé/Abstract:**
This invention is directed to methods of reducing immunoglobulin production (e.g. IgA, IgM, and/or IgG, etc.) in subjects diagnosed with an autoimmune disease and/or fibrosis comprising administering to the subjects compositions comprising sBCMA variants and/or sBCMA variant - Fc fusion proteins.

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Abstract:

This invention is directed to methods of reducing immunoglobulin production (e.g. IgA, IgM, and/or IgG, etc.) in subjects diagnosed with an autoimmune disease and/or fibrosis comprising administering to the subjects compositions comprising sBCMA variants and/or sBCMA variant – Fc fusion proteins.

METHODS OF REDUCING PRODUCTION OF IgA, IgM AND/OR IgG USING sBCMA VARIANTS AND FC FUSION PROTEINS THEREOF

I. FIELD OF THE INVENTION

[0001] This invention relates to methods of reducing immunoglobulin production (e.g. IgA, IgM, and/or IgG, etc.) in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects compositions comprising soluble B-cell maturation antigen (sBCMA) variants and/or sBCMA variant – Fc fusion proteins.

II. BACKGROUND OF THE INVENTION

[0002] B-cell maturation antigen (BCMA) is a member of the tumor necrosis factor receptor superfamily member. The amino acid sequence of the extracellular domain of BCMA is shown in Figure 30. For example, BCMA is a receptor for β-cell Activating Factor of the TNF family (BAFF) and A Proliferation Inducing Ligand (APRIL). Anti-BCMA antibodies, including an antibody drug conjugate (ADC), have shown initial success in treating cancer in early testing, as have BCMA bispecific T cell engaging antibodies and CAR-T constructs using BCMA.

[0003] BAFF is previously described in WO/0012964 and US 9,650,430 B2, which are incorporated by reference herein. The amino acid sequence of the extracellular domain of BAFF is shown in Figure 7. BAFF is a cell survival and maturation factor for B cells, and overproduction of BAFF is associated with systemic autoimmune disease. In humans, high levels of BAFF are detectable in the blood of a proportion of patients with autoimmune rheumatic diseases, particularly systemic lupus erythematosus and Sjögren's syndrome (Groom et al. *J. Clin. Invest.*, 2002,109:59; Zhang et al. *J. Immunol.*, 2001, 166:6; Cheema et al. *Arthritis Rheum.* 2001, 44:1313, which are all incorporated by reference herein). BAFF is also an effective costimulator for T cells, and this costimulation occurs entirely through BAFF-R (Ng et al. *J. Immunol.*, 2004, 173:807, incorporated by reference herein).

[0004] APRIL is previously described in WO 99 12965 and US 7,276,241 B2, which are incorporated by reference herein. The amino acid sequence of the extracellular domain

of APRIL is shown in Figure 30. APRIL expression and functional studies suggest that this protein is utilized by tumor cells to induce rapid proliferation. In addition, APRIL may act in other disease settings, for example, in cell proliferative diseases, such as those that occur in connection with some autoimmune diseases (*e.g.*, lupus) or in inflammatory diseases where cell populations expand rapidly (*e.g.* bacterial sepsis) (US 7,276,241B2, which is incorporated by reference herein).

[0005] Transmembrane activator and CAML interactor (TACI) also known as tumor necrosis factor receptor superfamily member 13B (TNFRSF13B) is a type III transmembrane protein. Several proteins (BAFF/BLys, APRIL, Syndecan-2) have been identified as TACI ligands. The interaction of TACI with its ligands induces activation of the transcription factors NFAT, AP1, and NF-κ B and plays a crucial role in humoral immunity by regulation of B cell proliferation and survival. TACI activation of B cells leads to their differentiation and maturation, including antibody isotype switch, and T cell-independent antibody production (Chinen et al. *J Allergy Clin Immunol.* 2011, 127(6): 1579, incorporated by reference herein).

[0006] APRIL and BAFF can bind to receptors, such as BCMA, BAFF-receptor (BAFFR) and TACI, and thus neutralizing APRIL and/or BAFF can be used for treating the diseases, e.g. cancers, autoimmune diseases and fibrosis arising from altered signaling pathways through BCMA, BAFFR and/or TACI.

[0007] Current treatments for autoimmune diseases and/or fibrotic disorders in patients especially those with elevated levels of immunoglobulin are inadequate due to poor efficacy, low impact on survivorship, toxicity that causes severe side effects, or combinations thereof. Therefore, there is a need to develop additional methods for treating autoimmune disease(s) and/or fibrosis in patients with elevated levels of IgA, IgM, and/or IgG. The present invention satisfies at least this need.

[0008] It is an object of the present invention to provide methods of reducing immunoglobulin production (e.g. IgA, IgM, and/or IgG, etc.) in subjects diagnosed with autoimmune disease(s) and/or fibrotic disorder(s) comprising administering to the subjects compositions comprising soluble B-cell maturation antigen (sBCMA) variants and/or sBCMA variant – Fc fusion proteins.

III. BRIEF SUMMARY OF THE INVENTION

[0009] The present invention provides *inter alia,* a method of reducing immunoglobulin production in a subject diagnosed with an autoimmune disease and/or fibrosis, said method comprising administering to the subject a therapeutically effective dose of a soluble B-cell maturation antigen (sBCMA) variant protein and/or sBCMA variant -Fc fusion protein. In some embodiments, the present invention provides *inter alia,* a method of reducing immunoglobulin production in a subject diagnosed with an autoimmune disease, said method comprising administering to the subject a therapeutically effective dose of an sBCMA variant protein. In some embodiments, the present invention provides *inter alia,* a method of reducing immunoglobulin production in a subject diagnosed with an autoimmune disease, said method comprising administering to the subject a therapeutically effective dose of an sBCMA variant -Fc fusion protein. In some embodiments, the present invention provides *inter alia,* a method of reducing immunoglobulin production in a subject diagnosed with fibrosis, said method comprising administering to the subject a therapeutically effective dose of an sBCMA variant protein. In some embodiments, the present invention provides *inter alia,* a method of reducing immunoglobulin production in a subject diagnosed with fibrosis, said method comprising administering to the subject a therapeutically effective dose of an sBCMA variant-Fc fusion protein.

[0010] The present invention provides *inter alia,* a method of reducing production of IgA, IgM, and/or IgG in a subject diagnosed with an autoimmune disease and/or fibrosis, said method comprising administering to the subject a therapeutically effective dose of a soluble B-cell maturation antigen (sBCMA) variant protein and/or sBCMA variant -Fc fusion protein. In some embodiments, the present invention provides *inter alia,* a method of reducing production of IgA, IgM, and/or IgG in a subject diagnosed with an autoimmune disease, said method comprising administering to the subject a therapeutically effective dose of an sBCMA variant protein. In some embodiments, the present invention provides *inter alia,* a method of reducing production of IgA, IgM, and/or IgG in a subject diagnosed with an autoimmune disease, said method comprising administering to the subject a therapeutically effective dose of an sBCMA variant -Fc fusion protein. In some embodiments, the present invention provides *inter alia,* a method of reducing production of IgA, IgM, and/or IgG in a subject diagnosed with fibrosis, said method comprising

administering to the subject a therapeutically effective dose of an sBCMA variant protein. In some embodiments, the present invention provides *inter alia,* a method of reducing production of IgA, IgM, and/or IgG in a subject diagnosed with fibrosis, said method comprising administering to the subject a therapeutically effective dose of an sBCMA variant-Fc fusion protein. In some embodiments, the method as disclosed herein reduces production of IgA. In some embodiments, the method as disclosed herein reduces production of IgM. In some embodiments, the method as disclosed herein reduces production of IgG. In some embodiments, the method as disclosed herein reduces production of both IgA and IgM. In some embodiments, the method as disclosed herein reduces production of both IgA and IgG. In some embodiments, the method as disclosed herein reduces production of both IgM and IgG. In some embodiments, the method as disclosed herein reduces production of IgA, IgM and IgG.

[0011] In one aspect, the invention provides a method of reducing production of IgA, IgM, and/or IgG in a subject diagnosed with an autoimmune disease or fibrosis, said method comprising administering to the subject a therapeutically effective dose of a soluble B-cell maturation antigen (sBCMA) variant-Fc fusion protein, wherein the sBCMA variant-Fc fusion protein comprises:

a) a variant sBCMA domain comprising at least one amino acid substitution as compared to SEQ ID NO:1, wherein said amino acid substitution is at a position number selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 14, 16, 19, 20, 22, 23, 25, 26, 29, 31, 32, 35, 36, 38, 39, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, and 54, wherein the numbering is according to the EU index;

b) an optional linker; and

c) an Fc domain.

[0012] In an additional aspect, the invention provides the method as disclosed herein, wherein normal B cell viability is not altered.

[0013] In a further aspect, the invention provides the method as disclosed herein, wherein the method reduces production of IgA.

[0014] In an additional aspect, the invention provides the method as disclosed herein, wherein the method reduces production of IgM.

[0015] In a further aspect, the invention provides the method as disclosed herein, wherein the method reduces production of IgG.

[0016] In a further aspect, the invention provides the method as disclosed herein, wherein the method reduces production of both IgA and IgM.

[0017] In a further aspect, the invention provides the method as disclosed herein, wherein the method reduces production of both IgA and IgG.

[0018] In a further aspect, the invention provides the method as disclosed herein, wherein the method reduces production of both IgM and IgG.

[0019] In a further aspect, the invention provides the method as disclosed herein, wherein the method reduces production of IgA, IgM and IgG.

[0020] In a further aspect, the invention provides the method as disclosed herein, wherein the subject is diagnosed with the autoimmune disease.

[0021] In an additional aspect, the invention provides the method as disclosed herein, wherein the autoimmune disease is selected from the group consisting of IgA Nephropathy, Systemic Lupus Erythematosus, Churg-Strauss Syndrome, Myasthenia Gravis, Multiple Sclerosis, and rheumatoid arthritis. In an additional aspect, the invention provides the method as disclosed herein, wherein the autoimmune disease is Lupus.

[0022] In a further aspect, the invention provides the method as disclosed herein, wherein the subject is diagnosed with the fibrosis.

[0023] In an additional aspect, the invention provides the method as disclosed herein, wherein the fibrosis is selected from the group consisting of idiopathic pulmonary fibrosis, non-alcoholic steatohepatitis, scleroderma, and kidney fibrosis.

[0024] In a further aspect, the invention provides the method as disclosed herein, wherein said fusion protein comprises, from N- to C-terminal:

a) said variant sBCMA domain;

b) said optional linker; and

c) said Fc domain.

[0025] In a further aspect, the invention provides the method as disclosed herein, wherein said fusion protein comprises, from N- to C-terminal:

a) said Fc domain;

b) said optional linker; and

c) said variant sBCMA domain.

[0026] In an additional aspect, the invention provides the method as disclosed herein, wherein said variant sBCMA domain has at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO:1.

[0027] In a further aspect, the invention provides the method as disclosed herein, wherein said amino acid substitution(s) occur at one of said positions, two of said positions, three of said positions, four of said positions, five of said positions, six of said positions, seven of said positions, eight of said positions, or nine of said positions.

[0028] In an additional aspect, the invention provides the method as disclosed herein, wherein said amino acid substitution(s) is selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16G, S16N, S16R, H19L, H19Y, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36A, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

[0029] In a further aspect, the invention provides the method as disclosed herein, wherein said amino acid substitution(s) is selected from the group consisting of M1V, L2S, Q3P, M4T, S9P, N11D, S16G, H19Y, N31S, N31D, T32I, T36A, R39H, N47S, K50E, and N53E.

[0030] In an additional aspect, the invention provides the method as disclosed herein, wherein said amino acid substitution(s) is selected from the group consisting of S16G, H19Y and T36A.

[0031] In a further aspect, the invention provides the method as disclosed herein, wherein said amino acid substitutions are selected from the group consisting of L2S/S9P/E12K/N31D/T36A/N42S/N53S, M1V/T32P/T36A/T46I/N53D/A54V, Q3R/S16N/T36A/A43T, F14L/S16G/T36A/V45A/N47D, M1T/M4V/S9F/S16G/T32A/Q38R, M1A/S9A/Q38R, G6E/Q25R/Q38R, M1V/M4I/G6E/S9P/N11D/V49M/T52M/A54V, N11D/S16G/N31S, N11D/H19Y/I22M/T32P/N47S/N53S, G6E/Q7R/H19Y/L35S, H19Y/N42D/S48P/T52A, M1V/N31D/T32I/T36A, M1V/A5T/H19L/T36A, M1T/N31D/T32A/T36A/Q38R/S44D/V49A/K50E, M1V/T36A/Q38R/A43V, M1V/L2S/S9P/Q10H/T36A/Q38R/K50G, T36A/Q38R/N53S, M1T/L2S/L35P/T36A/Q38R/T46A/K50R, A5T/A20V/T36A/Q38R, M1T/S16G/I22V/T36A/S44G/T46A/V49A, S16G/T36A, M1I/N11D/S16G/I22M/S29A/T36A/S44G/K50R, M1C/L2C/Q3R/M4E/N11D/S16G/T36P, M1I/N11D/S16G/I22M/S29A/T36A/S44G/K50R, N11D/N31D/T32I/T36A/S44N/N47D/N53D, M1R/L2C/Q3R, H19Y/T36A/S44G, H19Y/T32I/T36A/V49A, H19Y/N31S/T36A/V45A, H19Y/N31S/T36A, H19Y/T36P/T52A, H19Y/N31D/T52M, M1V/H19Y/V45M, S16G/H19Y/N47D, S16G/H19Y/K50T, S16G/H19Y/S44N/K50R, N11D/H19Y/S48T, S9P/N11D/S16R/T32A/Q38R/S44G/T46I/T52A/N53D/A54T, N11D/S16G/S44R, H19L/T32A/S44G/G51E/T52A, S16N/H19Y/T36A/K50R, M1V/H19Y/T36A/R39H/T46A, M1V/H19Y/T36A, H19Y/T36A/N42D/N47S/S48P, M1V/H19Y/T36A/S44G/N47D, M1V/H19Y/T36A/N42R/N53S, H19Y/L35P/T36A/N42D/T46I/V49A, Q3P/S9P/H19Y/N31S/T36A/R39H/N47R/K50E, M1V/H19Y/T36A/N42R/N53S, M1T/H19Y/T36A, M1V/S16N/H19Y/I22M/T36A, M1T/N11D/H19Y/T36A/N42S/V45A/N53S, N11D/S16G/H19Y/T36A/N47S/N53D, M1V/S9P/Q10P/S16G/H19Y/L26F/T36A/A43V/N53D, S16G/H19Y/T36A/V49A/N53D, S16G/T36A/A43T/S44G/V45M, M4V/S9P/S16G/T36A/Q38R, S9P/N11S/S16G/T36A/Q38R, N11D/E12K/S16R/T36A/T52M, M4V/T32I/T36A/Q38R/A43T/V45A/S48P, S9P/N11D/S16G/Q25R, M1T/A5T/S9P/S16G/Q25R/N31D/V49M, L2S/S9P/S16G/A20T/T32I/Q38R/N42D/T46A/S48L, S16G/Q25R/T46A, G6E/S9A/S16G/Q25R/N31D/N47S/T52M, H19Y/Q38R/T52M,

N11D/H19Y/I22M/T32P/N47S/N53S, S16G/H19Y/T36A, S16G/H19Y/T36A/N53D, S9P/N11D/S16G/H19Y/T36A/N47S/N53D, Q3P/S9P/H19Y/N31S/T36A/R39H/N47R/K50E, M1V/L2S/M4T/N11D/H19Y/T36A, M1V/L2S/M4T/N11D/T36A, M1V/L2S/M4T/H19Y/T36I/V45A/V49M, M1V/L2S/M4T/N11D/H19Y/T36A, M1V/L2S/M4T/S9P/Q10R/H19Y/T36A/T46A/N47S, M1V/L2S/M4T/S16G/N31D/T32I/T36A, M1V/M4T/T36A/Q38R/N53K, M1T/N11D/H19Y/T36A/N42S/V45A/N53S, M1T/N31D/T32A/T36A/A38R/S44D/V49A/K50E, M1T/S9P/P23S/Q38R/N42S/S48P/V49A/A54V, H19Y/T36A/S44G, H19Y/T36A, and M4T/T36A/Q38R/N42S/S44G/T46A/N47K/S48P/T52A.

[0032] In an additional aspect, the invention provides the method as disclosed herein, wherein said variant sBCMA domain comprises the amino acid substitutions S16G/H19Y/T36A, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

[0033] In a further aspect, the invention provides the method as disclosed herein, wherein said variant sBCMA domain comprises the amino acid substitutions S16G/H19Y/T36A/N53D, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53K, N53S, A54V, and A54T.

[0034] In an additional aspect, the invention provides the method as disclosed herein, wherein said variant sBCMA domain comprises the amino acid substitutions S9P/N11D/S16G/H19Y/T36A/N47S/N53D, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, Q10H, Q10P, Q10R, N11S, E12K, F14L, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53K, N53S, A54V, and A54T.

[0035] In a further aspect, the invention provides the method as disclosed herein, wherein said variant sBCMA domain comprises the amino acid substitutions Q3P/S9P/H19Y/N31S/T36A/R39H/N47R/K50E, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16G, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47S, S48L, S48P, S48T, V49A, V49M, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

[0036] In an additional aspect, the invention provides the method as disclosed herein, wherein said variant sBCMA domain comprises the amino acid substitutions M1V/L2S/M4T/S16G/N31D/T32I/T36A, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, L2C, Q3P, Q3R, M4E, M4I, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16N, S16R, H19L, H19Y, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31S, T32A, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

[0037] In a further aspect, the invention provides the method as disclosed herein, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 67.

[0038] In an additional aspect, the invention provides the method as disclosed herein, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 68.

[0039] In a further aspect, the invention provides the method as disclosed herein, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 69.

[0040] In an additional aspect, the invention provides the method as disclosed herein, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 49.

[0041] In a further aspect, the invention provides the method as disclosed herein, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 74.

[0042] In an additional aspect, the invention provides the method as disclosed herein, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 67.

[0043] In a further aspect, the invention provides the method as disclosed herein, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 68.

[0044] In an additional aspect, the invention provides the method as disclosed herein, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 69.

[0045] In a further aspect, the invention provides the method as disclosed herein, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 49.

[0046] In an additional aspect, the invention provides the method as disclosed herein, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 74.

[0047] In a further aspect, the invention provides the method as disclosed herein, wherein said Fc domain is a human IgG Fc domain or a variant human IgG Fc domain.

[0048] In an additional aspect, the invention provides the method as disclosed herein, wherein said human IgG Fc domain comprises the hinge-CH2-CH3 of human IgG1.

[0049] In a further aspect, the invention provides the method as disclosed herein, wherein said Fc domain is a variant human IgG Fc domain.

[0050] In an additional aspect, the invention provides the method as disclosed herein, wherein said Fc domain is a human IgG1 Fc domain.

[0051] In a further aspect, the invention provides the method as disclosed herein, wherein said linker is SEQ ID NO:87.

[0052] In an additional aspect, the invention provides the method as disclosed herein, wherein said linker is selected from the group consisting of (GS)n, (GSGGS)n, (GGGGS)n, and (GGGS)n, wherein n is selected from the group consisting of 1, 2, 3, 4 and 5.

[0053] In a further aspect, the invention provides the method as disclosed herein, wherein said linker is SEQ ID NO:88.

[0054] In an additional aspect, the invention provides the method as disclosed herein, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:80.

[0055] In a further aspect, the invention provides the method as disclosed herein, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:81.

[0056] In an additional aspect, the invention provides the method as disclosed herein, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:82.

[0057] In a further aspect, the invention provides the method as disclosed herein, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:83.

[0058] In an additional aspect, the invention provides the method as disclosed herein, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:84.

IV. BRIEF DESCRIPTION OF THE DRAWINGS

[0059] **Figure 1** shows nonhuman single dose toxicity study design.

[0060] **Figure 2** shows immune cell counts in male cynomolgus monkeys in single dose toxicity studies treated with vehicle control and variant sBCMA Fc at 0.1mg/kg, 1mg/kg, 10mg/kg and 100mg/kg. **Figure 2A**, CD3+CD4+ T Lymphocyte. **Figure 2B**,

CD3+CD8+ Cytotoxic T Cells. **Figure 2C,** CD3-CD16+ NK Cells. **Figure 2D,** CD3-CD19+ Pan B Cells. **Figure 2E,** CD3-CD20+ Mature B Cells.

[0061] **Figure 3** shows immune cell counts in female cynomolgus monkeys in single dose toxicity studies treated with vehicle control and variant sBCMA Fc at 0.1mg/kg, 1mg/kg, 10mg/kg and 100mg/kg. **Figure 3A**, CD3+CD4+ T Lymphocyte. **Figure 3B**, CD3+CD8+ Cytotoxic T Cells. **Figure 3C,** CD3-CD16+ NK Cells. **Figure 3D,** CD3-CD19+ Pan B Cells. **Figure 3E,** CD3-CD20+ Mature B Cells.

[0062] **Figure 4** shows body weight over time in male **4A** and female **4B** cynomolgus monkeys in single dose toxicity studies treated with vehicle control and variant sBCMA Fc at 0.1mg/kg, 1mg/kg, 10mg/kg and 100mg/kg.

[0063] **Figure 5** shows total lymphocyte counts over time in male **5A** and female **5B** cynomolgus monkeys in single dose toxicity studies treated with vehicle control and variant sBCMA Fc at 0.1mg/kg, 1mg/kg, 10mg/kg and 100mg/kg.

[0064] **Figure 6** shows changes of immunoglobulin levels over time in female cynomolgus monkeys in single dose toxicity studies treated with vehicle control and variant sBCMA Fc at 0.1mg/kg, 1mg/kg, 10mg/kg and 100mg/kg.

[0065] **Figure 7** shows changes of immunoglobulin over time in male cynomolgus monkeys in single dose toxicity studies treated with vehicle control and variant sBCMA Fc at 0.1mg/kg, 1mg/kg, 10mg/kg and 100mg/kg.

[0066] **Figure 8** shows hematology panel I in male cynomolgus monkeys in single dose toxicity studies treated with vehicle control and variant sBCMA Fc at 0.1mg/kg, 1mg/kg, 10mg/kg and 100mg/kg. Abbreviations: RBC (Red Blood Cells), HGB (Hemoglobin), HCT (Hematocrit), MCV (Mean Corpuscular Volume), MCH (Mean Corpuscular Hemoglobin), MCHC (Mean Corpuscular Hemoglobin Concentration), RDW (Red Cell Distribution Width), RET (Reticulocytes (Absolute)).

[0067] **Figure 9** shows hematology panel II in male cynomolgus monkeys in single dose toxicity studies treated with vehicle control and variant sBCMA Fc at 0.1mg/kg, 1mg/kg, 10mg/kg and 100mg/kg. Abbreviations: PLT (Platelets), WBC (White Blood Cells), NEUT (Neutrophils (Absolute)), LYMP (Lymphocytes (Absolute)), MONO (Monocytes (Absolute)), EOS (Eosinophils (Absolute)), BASO (Basophils (Absolute)).

[0068] **Figure 10** shows hematology panel I in female cynomolgus monkeys in single dose toxicity studies treated with vehicle control and variant sBCMA Fc at 0.1mg/kg, 1mg/kg, 10mg/kg and 100mg/kg. Abbreviations: RBC (Red Blood Cells), HGB (Hemoglobin), HCT (Hematocrit), MCV (Mean Corpuscular Volume), MCH (Mean Corpuscular Hemoglobin), MCHC (Mean Corpuscular Hemoglobin Concentration), RDW (Red Cell Distribution Width), RET (Reticulocytes (Absolute)).

[0069] **Figure 11** shows hematology panel II in female cynomolgus monkeys in single dose toxicity studies treated with vehicle control and variant sBCMA Fc at 0.1mg/kg, 1mg/kg, 10mg/kg and 100mg/kg. Abbreviations: PLT (Platelets), WBC (White Blood Cells), NEUT (Neutrophils (Absolute)), LYMP (Lymphocytes (Absolute)), MONO (Monocytes (Absolute)), EOS (Eosinophils (Absolute)), BASO (Basophils (Absolute)).

[0070] **Figure 12** shows coagulation panel in male cynomolgus monkeys in single dose toxicity studies treated with vehicle control and variant sBCMA Fc at 0.1mg/kg, 1mg/kg, 10mg/kg and 100mg/kg. Abbreviations: PT (Prothrombin Time), APTT (Activated Partial Thromboplastin Time), FIB (Fibrinogen).

[0071] **Figure 13** shows coagulation panel in female cynomolgus monkeys in single dose toxicity studies treated with vehicle control and variant sBCMA Fc at 0.1mg/kg, 1mg/kg, 10mg/kg and 100mg/kg. Abbreviations: PT (Prothrombin Time), APTT (Activated Partial Thromboplastin Time), FIB (Fibrinogen).

[0072] **Figure 14** shows chemistry panel I in male cynomolgus monkeys in single dose toxicity studies treated with vehicle control and variant sBCMA Fc at 0.1mg/kg, 1mg/kg, 10mg/kg and 100mg/kg. Abbreviations: ALT (Alanine Aminotransferase), AST (Aspartate Aminotransferase), ALP (Alkaline Phosphatase), GGT (Gamma Glutamyl Transferase), CK (Creatine Kinase), TBIL (Total Bilirubin), GLU (Glucose).

[0073] **Figure 15** shows chemistry panel II in male cynomolgus monkeys in single dose toxicity studies treated with vehicle control and variant sBCMA Fc at 0.1mg/kg, 1mg/kg, 10mg/kg and 100mg/kg. Abbreviations: UREA (Urea), CREA (Creatinine), TG (Triglycerides), CHOL (Total Cholesterol), TP (Total Protein), ALB (Albumin), GLOB (Globulin).

[0074] **Figure 16** shows chemistry panel III in male cynomolgus monkeys in single dose toxicity studies treated with vehicle control and variant sBCMA Fc at 0.1mg/kg, 1mg/kg, 10mg/kg and 100mg/kg. Abbreviations: A/G (Albumin/Globulin Ratio), Na (Sodium), K (Potassium Chloride), Cl (Chloride), IgA (Immunoglobulin A), IgG (Immunoglobulin G), IgM (Immunoglobulin M).

[0075] **Figure 17** shows chemistry panel I in female cynomolgus monkeys in single dose toxicity studies treated with vehicle control and variant sBCMA Fc at 0.1mg/kg, 1mg/kg, 10mg/kg and 100mg/kg. Abbreviations: ALT (Alanine Aminotransferase), AST (Aspartate Aminotransferase), ALP (Alkaline Phosphatase), GGT (Gamma Glutamyl Transferase), CK (Creatine Kinase), TBIL (Total Bilirubin), GLU (Glucose).

[0076] **Figure 18** shows chemistry panel II in female cynomolgus monkeys in single dose toxicity studies treated with vehicle control and variant sBCMA Fc at 0.1mg/kg, 1mg/kg, 10mg/kg and 100mg/kg. Abbreviations: UREA (Urea), CREA (Creatinine), TG (Triglycerides), CHOL (Total Cholesterol), TP (Total Protein), ALB (Albumin), GLOB (Globulin).

[0077] **Figure 19** shows chemistry panel III in female cynomolgus monkeys in single dose toxicity studies treated with vehicle control and variant sBCMA Fc at 0.1mg/kg, 1mg/kg, 10mg/kg and 100mg/kg. Abbreviations: A/G (Albumin/Globulin Ratio), Na (Sodium), K (Potassium Chloride), Cl (Chloride), IgA (Immunoglobulin A), IgG (Immunoglobulin G), IgM (Immunoglobulin M).

[0078] **Figure 20** shows cytokine panel I in male cynomolgus monkeys in single dose toxicity studies treated with vehicle control and variant sBCMA Fc at 0.1mg/kg, 1mg/kg, 10mg/kg and 100mg/kg. Abbreviations: PrD0M (Pre Dose 0 min), 1HPD (1 Hr Post Dose), 3HPD (3 Hr Post Dose), 8HPD (8 Hr Post Dose).

[0079] **Figure 21** shows cytokine panel II in male cynomolgus monkeys in single dose toxicity studies treated with vehicle control and variant sBCMA Fc at 0.1mg/kg, 1mg/kg, 10mg/kg and 100mg/kg. Abbreviations: PrD0M (Pre Dose 0 min), 1HPD (1 Hr Post Dose), 3HPD (3 Hr Post Dose), 8HPD (8 Hr Post Dose).

[0080] **Figure 22** shows cytokine panel I in female cynomolgus monkeys in single dose toxicity studies treated with vehicle control and variant sBCMA Fc at 0.1mg/kg,

1mg/kg, 10mg/kg and 100mg/kg. Abbreviations: PrD0M (Pre Dose 0 min), 1HPD (1 Hr Post Dose), 3HPD (3 Hr Post Dose), 8HPD (8 Hr Post Dose).

[0081] **Figure 23** shows cytokine panel II in female cynomolgus monkeys in single dose toxicity studies treated with vehicle control and variant sBCMA Fc at 0.1mg/kg, 1mg/kg, 10mg/kg and 100mg/kg. Abbreviations: PrD0M (Pre Dose 0 min), 1HPD (1 Hr Post Dose), 3HPD (3 Hr Post Dose), 8HPD (8 Hr Post Dose).

[0082] **Figure 24A** shows viable cell density of sBCMA variant clone pools at 11 days during Feb batch culture. Each line represents cell growth of pooled clones grown in HyCell CHO or BalanCD CHO. **Figure 24B** shows viability of sBCMA variant clone pools at 11 days during Feb batch culture. Each line represents cell growth of pooled clones grown in HyCell CHO or BalanCD CHO.

[0083] **Figure 25** shows ProA-purified materials and glycosylation study of sBCMA variant clones in HyCell CHO or BalanCD CHO in the presence and the absence of PNGaseF using SDS-PAGE in non-Reduced (top) or Reduced (bottom) form.

[0084] **Figure 26** shows titer, IVCD and viability of sBCMA variant single cell clones at 12 day Fed batch experiment. IVCD (The Integral of Viable Cell Density).

[0085] **Figure 27** shows N-glycan profiles of sBCMA variant top 10 clones at 12 day Fed batch experiment.

[0086] **Figures 28A-28D** show the sequences of sBCMA variant clones as compared to the sequence of the extracellular domain of wild-type human BCMA as set forth in SEQ ID NO:1. **Figure 28A** shows the sequences of S3 clones# 1-12. **Figure 28B** shows the sequences of S4 clones# 13-41. **Figure 28C** shows the sequences of S5 clones# 42-74. **Figure 28D** shows the sequences of S6 clones# 75-118.

[0087] **Figure 29** shows the amino acid sequences of sBCMA variant – Fc fusion proteins as set forth in SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, and SEQ ID NO:84. The variant sBCMA domain is underlined, the linker domain is bolded and the human IgG1 Fc domain is italic.

[0088] **Figure 30** shows the amino acid sequences of the extracellular domain of wild type human BCMA (SEQ ID NO:1), the extracellular domain of APRIL (SEQ ID NO:85),

the extracellular domain of BAFF (SEQ ID NO:86), a linker domain (SEQ ID NO:87) and another linker domain (SEQ ID NO:88).

[0089] **Figures 31 and 32** show results from evaluation of sBCMA Variants on lupus model in NZBWF1/J mice + Pristane

V. DETAILED DESCRIPTION OF THE INVENTION

[0090] In order to more clearly and concisely point out the subject matter of the claimed invention, the following definitions are provided for specific terms used in the following written description and appended claims.

A. Introduction

[0091] The present invention is directed to the use of soluble forms of human BCMA that contain amino acid modifications, e.g. variant sBCMA proteins. These variant sBCMA proteins bind to either one or both of the BCMA ligands, human BAFF and/or human APRIL, with tighter affinity than wild type human BCMA. APRIL and BAFF can bind to receptors, such as BCMA, BAFFR and TACI, and thus neutralizing APRIL and/or BAFF can be used for treating diseases arising from altered signaling pathways through BCMA, BAFFR and/or TACI. These diseases include autoimmune diseases and fibrosis. Neutralizing APRIL alone can be effective in treating autoimmune diseases and fibrosis expressing high levels of BCMA and TACI or other receptors that are activated through binding to APRIL. Neutralizing BAFF alone can be effective in treating fibrosis and autoimmune diseases expressing BCMA, BAFFR and TACI or other receptors that are activated through binding to BAFF. Therefore, the variant sBCMA as described herein can be used to treat immunomodulatory disorders and/or fibrotic diseases expressing BCMA, BAFFR, TACI and/or any other receptors that are activated through binding to APRIL and/or BAFF by binding more tightly, and thus preferentially, to the ligand(s) e.g. APRIL and/or BAFF and thus altering the normal receptor signaling that would otherwise occur between BCMA, BAFFR and/or TACI on the surface of a cell with APRIL or BAFF.

[0092] In some embodiments, the present invention provides methods of reducing immunoglobulin production in subjects diagnosed with autoimmune disease(s) and/or

fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant protein(s). In some embodiments, the present invention provides methods of reducing production of IgA, IgM and/or IgG in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant protein(s).

[0093] In some embodiments, the present invention provides methods of reducing production of IgA, IgM or both in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant protein(s). In some embodiments, the present invention provides methods of reducing production of IgA, IgG or both in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant protein(s). In some embodiments, the present invention provides methods of reducing production of IgG, IgM or both in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant protein(s).

[0094] In some embodiments, the present invention provides methods of reducing production of IgA in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant protein(s). In some embodiments, the present invention provides methods of reducing production of IgM in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant protein(s). In some embodiments, the present invention provides methods of reducing production of IgG in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant protein(s).

[0095] In some embodiments, the present invention provides methods of reducing production of IgA and IgM in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant protein(s). In some embodiments, the present invention provides methods of reducing production of IgA and IgG in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant

protein(s). In some embodiments, the present invention provides methods of reducing production of IgG and IgM in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant protein(s). In some embodiments, the present invention provides methods of reducing production of IgA, IgM and IgG in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant protein(s).

[0096] Additionally, in some embodiments, since the sBCMA variants are small proteins that generally are cleared rapidly from the bloodstream, the invention provides fusion proteins that link the sBCMA variant to a human or variant Fc domain as discussed herein. Since Fc domains, through binding to the FcRn receptor, confer extended half-life in serum, the creation of an sBCMA variant-Fc domain fusion proteins results in improved therapies. Thus, the invention provides sBCMA domain-Fc domain fusion proteins, referred sometimes herein as "fusion proteins". In some embodiments, the sBCMA variant or the variant sBCMA domain of the fusion protein as described herein exhibits enhanced binding affinity for APRIL as compared to SEQ ID NO:1. In some embodiments, the sBCMA variant or the variant sBCMA domain of the fusion protein as described herein exhibits enhanced binding affinity for BAFF as compared to SEQ ID NO:1. In some embodiments, the sBCMA variant or the variant sBCMA domain of the fusion protein as described herein exhibits enhanced binding affinity for APRIL and BAFF as compared to SEQ ID NO:1.

[0097] In some embodiments, the present invention provides methods of reducing immunoglobulin production in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s). In some embodiments, the present invention provides methods of reducing production of IgA, IgM and/or IgG in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s).

[0098] In some embodiments, the present invention provides methods of reducing production of IgA, IgM or both in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s). In some embodiments, the present invention provides methods

of reducing production of IgA, IgG or both in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s). In some embodiments, the present invention provides methods of reducing production of IgG, IgM or both in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s).

[0099] In some embodiments, the present invention provides methods of reducing production of IgA in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s). In some embodiments, the present invention provides methods of reducing production of IgM in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s). In some embodiments, the present invention provides methods of reducing production of IgG in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s).

[00100] In some embodiments, the present invention provides methods of reducing production of IgA and IgM in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s). In some embodiments, the present invention provides methods of reducing production of IgA and IgG in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s). In some embodiments, the present invention provides methods of reducing production of IgG and IgM in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s). In some embodiments, the present invention provides methods of reducing production of IgA, IgM and IgG in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s).

B. Definitions

[00101] As used herein, the following terms have the meanings ascribed to them unless specified otherwise.

[00102] The terms "a", "an", or "the" as used herein not only include aspects with one member, but also include aspects with more than one member. For instance, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a cell" includes a plurality of such cells and reference to "the agent" includes reference to one or more agents known to those skilled in the art, and so forth.

[00103] As used herein, "protein" herein is meant at least two covalently attached amino acids, which includes proteins, polypeptides, oligopeptides and peptides.

[00104] The term "isolated" refers to a molecule that is substantially free of its natural environment and devoid of other proteins. For instance, an isolated protein is substantially free of cellular material or other proteins from the cell or tissue source from which it is derived. The term "isolated" also refers to preparations where the isolated protein is sufficiently pure to be administered as a pharmaceutical composition, or at least about 70-80%, 80-90%, or 90-95% (w/w) pure, or at least about 95%, 96%, 97%, 98%, 99%, or 100% (w/w) pure. In particular, it is preferred that the polypeptides are in "essentially pure form", i.e., that the polypeptide preparation is essentially free of other polypeptide material with which it is natively associated. This can be accomplished, for example, by preparing the polypeptide by means of well-known recombinant methods or by classical purification methods.

[00105] The term B-cell maturation antigen "BCMA" refers to the protein for B cell maturation as described in Gras et al. *International Immunology,* 1995, 7:1093; Y. Laabi et al. *EMBO J.*, 1992, 11:3897. BCMA is a member of the TNF-receptor superfamily. For example, BCMA is a receptor for APRIL and BAFF. The amino acid sequence of the extracellular domain of the wild type human BCMA (SEQ ID NO:1) is shown in Table 3 and Figure 30.

[00106] The term "ligand" refers to a biomolecule that is able to bind to and form a complex with a second biomolecule such as a receptor present on the surface of target cells to serve a biological purpose. A ligand is generally an effector molecule that binds to a site

on a target protein, *e.g.*, by intermolecular forces such as ionic bonds, hydrogen bonds, hydrophobic interactions, dipole-dipole bonds, or Van der Waals forces. In the present invention, APRIL and BAFF are ligand proteins.

[00107] The term "receptor" refers to a biomolecule present on the surface of a target cell that is able to bind to and form a complex with a second biomolecule such as a ligand. A receptor generally activates a specific signal transduction pathway. For example, BCMA is a receptor for APRIL and BAFF, members of the TNF family.

[00108] By "position" as used herein is meant a location in the sequence of a protein. In some embodiments of the present invention, positions are numbered sequentially starting with the first amino acid of the mature protein, for example for the human BCMA protein shown in Figure 28. In some cases, for example for the Fc domain portion of the fusion proteins described herein, the Fc domain positions may be numbered sequentially, or according to an established format, for example the EU index. The EU index or EU index as in Kabat or EU numbering scheme refers to the EU numbering (see SEQUENCES OF IMMUNOLOGICAL INTEREST, 5th edition, NIH publication, No. 91-3242, E.A. Kabat et al., entirely incorporated by reference; and see also Edelman et al., 1969, Proc Natl Acad Sci USA 63:78-85, hereby entirely incorporated by reference).

[00109] By "amino acid modification" or "amino acid sequence modification" herein is meant an amino acid substitution, insertion, and/or deletion in a polypeptide sequence.

[00110] By "parent protein" as used herein is meant a starting protein that is subsequently modified to generate a variant. The parent protein may be a naturally occurring protein, or a variant or engineered version of a naturally occurring protein. Parent protein may refer to the protein itself, compositions that comprise the parent protein, or the amino acid sequence that encodes it. In this context, a "parent Fc domain" will be relative to the recited variant; thus, a "variant human IgG Fc domain" is compared to the parent Fc domain of human IgG, for example, a "variant human IgG1 Fc domain" is compared to the parent Fc domain of human IgG1, *etc.*

[00111] By "wild type" or "WT" herein is meant an amino acid sequence or a nucleotide sequence that is found in nature, including allelic variations. A WT protein has an

amino acid sequence or a nucleotide sequence that has not been intentionally modified into a non-naturally occurring sequence.

[00112] By "variant protein" or "protein variant", or "variant" as used herein is meant a protein with an amino acid sequence which differs from that of a parent protein by virtue of at least one amino acid sequence modification. For example, "variant sBCMA" or "sBCMA variant" as used herein is meant a protein with an amino acid sequence which differs from that of a parent sBCMA protein by virtue of at least one amino acid sequence modification yet still retains the ability to bind to a cognate ligand, as outlined below. In some embodiments, the parent proteins are human wild type sequences. In some embodiments, the parent proteins are human sequences with variants. Protein variant may refer to the protein itself, a composition comprising the protein, or the amino sequence that encodes it. In some embodiments, the protein variant has amino acid substitution(s) at one position, two positions, three positions, four positions, five positions, six positions, seven positions, eight positions, nine positions or ten positions. The protein variant sequence herein will possess at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, or 98% sequence identity with a parent protein sequence, and preferably at least about 85%, 86%, 88%, 90%, 93% or 95% sequence identity. The relatedness between two amino acid sequences or between two nucleotide sequences is described by the parameter "sequence identity" or "identity". The degree of identity between an amino acid sequence of the present invention ("invention sequence") and the parent amino acid sequence referred to in the claims (e.g. SEQ ID NO:1) is calculated as the number of exact matches in an alignment of the two sequences, divided by the length of the "invention sequence," or the length of the parent amino acid sequence, whichever is the shortest. The result is expressed in percent identity as calculated below.

[00113] For purposes of the present invention, the extracellular domain of sBCMA as set forth in SEQ ID NO:1 is used as a parent protein to determine the corresponding amino acid sequence modification in sBCMA variants. The amino acid sequence of an sBCMA variant protein is aligned with the amino acid sequence of SEQ ID NO:1, and based on the alignment, the amino acid position number corresponding to any amino acid residue as disclosed in SEQ ID NO:1 is determined using the Needleman-Wunsch algorithm (Needleman and Wunsch, 1970, J. Mol. Biol. 48: 443-453) as implemented in the Needle

program of the EMBOSS package (EMBOSS: The European Molecular Biology Open Software Suite, Rice et al., 2000, Trends Genet. 16: 276-277), preferably version 5.0.0 or later. The parameters used are gap open penalty of 10, gap extension penalty of 0.5, and the EBLOSUM62 (EMBOSS version of BLOSUM62) substitution matrix. The output of Needle labeled "longest identity" (obtained using the -nobrief option) is used as the percent identity and is calculated as follows:

[00114] (Identical Residues x 100)/(Length of Alignment - Total Number of Gaps in Alignment)

[00115] Identification of the corresponding amino acid residue in another sBCMA variant can be determined by an alignment of multiple polypeptide sequences using several computer programs including, but not limited to, MUSCLE (multiple sequence comparison by log-expectation; version 3.5 or later; Edgar, 2004, Nucleic Acids Research 32: 1792-1797), MAFFT (version 6.857 or later; Katoh and Kuma, 2002, Nucleic Acids Research 30: 3059-3066; Katoh et al. , 2005, Nucleic Acids Research 33: 51 1 -518; Katoh and Toh, 2007, Bioinformatics 23: 372-374; Katoh et al., 2009, Methods in Molecular Biology 537: 39-64; Katoh and Toh, 2010, Bioinformatics 26: 1899-1900), EMBOSS EMMA employing ClustalW (1.83 or later; Thompson et al., 1994, Nucleic Acids Research 22: 4673-4680), and EMBL-EBI employing Clustal Omega (Sievers and Higgins, 2014, Methods Mol Biol. 2014;1079:105–16), using their respective default parameters.

[00116] When the other variant polypeptides have diverged from the wild type sBCMA such that traditional sequence-based comparison fails to detect their relationship (Lindahl and Elofsson, 2000, J. Mol. Biol. 295: 613-615), other pairwise sequence comparison algorithms can be used. Greater sensitivity in sequence-based searching can be attained using search programs that utilize probabilistic representations of polypeptide families (profiles) to search databases. For example, the PSI-BLAST program generates profiles through an iterative database search process and is capable of detecting remote homologs (Atschul et al., 1997, Nucleic Acids Res. 25: 3389-3402). Even greater sensitivity can be achieved if the family or superfamily for the polypeptide has one or more representatives in the protein structure databases. Programs such as GenTHREADER (Jones, 1999, J. Mol. Biol. 287: 797-815; McGuffin and Jones, 2003, Bioinformatics 19: 874-881) utilize information from a variety of sources (PSI-BLAST, secondary structure prediction,

structural alignment profiles, and solvation potentials) as input to a neural network that predicts the structural fold for a query sequence. Similarly, the method of Gough et al., 2000, J. Mol. Biol. 313: 903-919, can be used to align a sequence of unknown structure with the superfamily models present in the SCOP database. These alignments can in turn be used to generate homology models for the polypeptide, and such models can be assessed for accuracy using a variety of tools developed for that purpose.

[00117] For proteins of known structure, several tools and resources are available for retrieving and generating structural alignments. For example, the SCOP superfamilies of proteins have been structurally aligned, and those alignments are accessible and downloadable. Two or more protein structures can be aligned using a variety of algorithms such as the distance alignment matrix (Holm and Sander, 1998, Proteins 33: 88-96) or combinatorial extension (Shindyalov and Bourne, 1998, Protein Engineering 11: 739-747), and implementation of these algorithms can additionally be utilized to query structure databases with a structure of interest in order to discover possible structural homologs (e.g., Holm and Park, 2000, Bioinformatics 16: 566-567).

[00118] In describing the variants of the present invention, the nomenclature described below is adapted for ease of reference. The standardly accepted IUPAC single letter or three letter amino acid abbreviation is employed.

[00119] For an amino acid substitution, the following nomenclature is used herein: Original amino acid, position, substituted amino acid. Accordingly, the substitution of alanine at position 43 with valine is designated as "Ala43Val" or "A43V". Multiple mutations are separated by forward slash marks ("/"), e.g., "N11D/S16G/N31S", representing substitutions at positions 11, 16 and 31, respectively. . The name, 3-letter abbreviation, and 1-letter abbreviation for each of the 20 amino acids is shown in Table 1.

[00120] **Table 1.** The name, 3-letter abbreviation, and 1-letter abbreviation for each of the 20 amino acids.

Amino Acid	3-Letter Code	1-Letter Code
Alanine	Ala	A
Cysteine	Cys	C
Aspartic acid or aspartate	Asp	D
Glutamic acid or glutamate	Glu	E
Phenylalanine	Phe	F
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Lysine	Lys	K
Leucine	Leu	L
Methionine	Met	M
Asparagine	Asn	N
Proline	Pro	P
Glutamine	Gln	Q
Arginine	Arg	R
Serine	Ser	S
Threonine	Thr	T
Valine	Val	V
Tryptophan	Trp	W
Tyrosine	Tyr	Y

[00121] The term "nucleic acid construct" refers to a nucleic acid molecule, either single-stranded or double-stranded, which is isolated from a naturally occurring gene or is modified to contain segments of nucleic acids in a manner that would not otherwise exist in nature or which is synthetic, and which comprises one or more control sequences.

[00122] The term "operably linked" refers to a configuration in which a control sequence is placed at an appropriate position relative to the coding sequence of a polynucleotide such that the control sequence directs expression of the coding sequence.

[00123] "Fc variant" or "variant Fc" as used herein is meant a protein comprising at least one amino acid sequence modification as compared to a parental Fc domain. In some embodiments, the parent Fc domain, is a human wild type Fc sequence, such as the Fc region from IgG1, IgG2, or IgG3. In some embodiments, the parent Fc domains are human Fc sequences with variants. For all positions discussed in the present invention that relate to the Fc domain of a human IgG, unless otherwise noted, amino acid position numbering is

according to the EU index. The modification can be an addition, deletion, substitution or any combination thereof as outlined herein. Alternatively, the variant Fc domains can have from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 amino acid modifications as compared to the parental Fc domain. Additionally, as discussed herein, the variant Fc domains herein still retain the ability to form a dimer with another Fc domain as well as bind to the FcRn receptor as measured using known techniques as described herein, such as non-denaturing gel electrophoresis.

[00124] The term "soluble BCMA" or "sBCMA" herein is meant a soluble portion of BCMA containing the extracellular domain (ECD) or a fragment or truncated version thereof, but not the entirety of the transmembrane domain or the cytoplasmic (intracellular) domain of BCMA. The ECD of human wild type sBCMA is shown as SEQ ID NO:1. In some embodiments, the parent wild type sBCMA domain can have N-terminal and/or C terminal truncations as long as the truncated wild type sBCMA retains biological activity, *e.g.* binding to APRIL and/or BAFF, as discussed below.

[00125] The term "sBCMA variant" or "variant sBCMA" refers to a variant of a parent sBCMA protein by virtue of at least one amino acid sequence modification. In some embodiments, the parent protein is a human wild type sBCMA. In some embodiments, the sBCMA variant retains specific binding to TGF family member(s), such as APRIL and/or BAFF, but has amino acid sequence modifications, e.g. amino acid substitutions, and can have N- or C-terminal truncations as compared to wild type sBCMA. Specific binding in this case is determined by any appropriate binding assay, such as ELISA, Biacore, Sapidyne KinExA, or Flow Cytometry binding analysis, which assays can also be used to determine binding affinity as outlined below. As discussed herein, sBCMA variants may have, in some instances, increased binding affinity for TGF family members (*e.g.* APRIL and/or BAFF) as compared to wild type sBCMA.

[00126] The term "binding affinity" refers to the ability of a ligand or variant thereof to form coordinated bonds with a protein, *e.g.*, a receptor or a variant thereof. The binding affinity between a ligand and protein can be represented by an equilibrium dissociation constant (Kd), a ratio of koff/kon between the ligand and the protein (*e.g.*, receptor or a variant thereof). Kd and binding affinity are inversely related. For instance, the Kd value relates the concentration of the sBCMA variant needed to bind to a TGF family member,

and a lower Kd value (lower sBCMA variant concentration) corresponds to a higher binding affinity for the TGF family member. A high binding affinity corresponds to a greater intermolecular force between the ligand and the protein. A low binding affinity corresponds to a lower intermolecular force between the ligand and the protein. In some cases, an increase in ligand binding affinity can be represented as a decrease of the off-rate by, for example, at least 1.4-fold, at least 1.6-fold, at least 1.8-fold, 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, at least 10-fold, at least 20-fold, at least 50-fold, at least 100-fold, at least 200-fold, at least 500-fold, or more.

[00127] "Specific binding" or "specifically binds to" or is "specific for" a particular ligand or variant thereof means binding that is measurably different from a non-specific interaction. Specific binding can be measured, for example, by determining binding of a molecule compared to binding of a control molecule, which generally is a molecule of similar structure that does not have binding activity. For example, specific binding can be determined by competition with a control molecule that is similar to the target. In some embodiments, the binding affinity is measured using any appropriate assay as would be understood by those skilled in the art as discussed above, such as a standard Biacore assay.

[00128] Specific binding for a particular ligand or variant thereof can be exhibited, for example, by a protein having a Kd for another ligand protein of at least about 10^{-4} M, at least about 10^{-5} M, at least about 10^{-6} M, at least about 10^{-7} M, at least about 10^{-8} M, at least about 10^{-9} M, alternatively at least about 10^{-10} M, at least about 10^{-11} M, at least about 10^{-12} M, at least about 10^{-15} M, or greater, where Kd refers to a dissociation rate of a particular protein-ligand interaction. In some embodiments, the variant sBCMA(s) of the present invention bind(s) a ligand with a binding affinity that is 1.5-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 15-, 20-, 50-, 100-, 200-, 500-, 1000-, 5,000-, 10,000- or more times greater as compared with a control molecule.

[00129] By "residue" as used herein is meant a position in a protein and its associated amino acid identity. For example, Asparagine 297 (also referred to as Asn297 or N297) is a residue at position 297 in the human antibody IgG1.

[00130] By "hinge" or "hinge region" or "antibody hinge region" or "hinge domain" herein is meant the flexible polypeptide comprising the amino acids between the first and

second constant domains of an antibody. Structurally, the IgG CH1 domain ends at EU position 215, and the IgG CH2 domain begins at residue EU position 231. Thus for IgG, the antibody hinge is herein defined to include positions 216 (E216 in IgG1) to 230 (p230 in IgG1), wherein the numbering is according to the EU index as in Kabat. In some cases, a "hinge fragment" is used, which contains fewer amino acids at either or both of the N- and C-termini of the hinge domain. As outlined herein, in some cases, Fc domains inclusive of the hinge are used, with the hinge generally being used as a flexible linker. (Additionally, as further described herein, additional flexible linker components can be used either with or without the hinge).

[00131] By "Fc" or "Fc region" or "Fc domain" as used herein is meant the polypeptide comprising the CH2-CH3 domains of an IgG molecule, and in some cases, inclusive of the hinge. In EU numbering for human IgG1, the CH2-CH3 domain comprises amino acids 231 to 447, and the hinge is 216 to 230. Thus the definition of "Fc domain" includes both amino acids 231-447 (CH2-CH3) or 216-447 (hinge-CH2-CH3), or fragments thereof. Thus Fc refers to the last two constant region immunoglobulin domains of IgA, IgD, and IgG, the last three constant region immunoglobulin domains of IgE and IgM, and in some cases, includes the flexible hinge N-terminal to these domains. For IgA and IgM, Fc may include the J chain. For IgG, the Fc domain comprises immunoglobulin domains Cγ2 and Cγ3 and in some cases, includes the lower hinge region between Cγ1 and Cγ2. An "Fc fragment" in this context may contain fewer amino acids from either or both of the N- and C-termini but still retains the ability to form a dimer with another Fc domain or Fc fragment as can be detected using standard methods, generally based on size (*e.g.* non-denaturing chromatography, size exclusion chromatography, *etc*). Human IgG Fc domains are of particular use in the present invention, and can be the Fc domain from human IgG1, IgG2, or IgG3. In general, IgG1 and IgG2 are used more frequently than IgG3. In some embodiments, amino acid sequence modifications are made to the Fc region, for example to alter binding to one or more FcγR receptors or to the FcRn receptor, and/or to increase the half-life *in vivo*.

[00132] By "IgG subclass modification" or "isotype modification" as used herein is meant an amino acid sequence modification that exchanges one amino acid of one IgG isotype to the corresponding amino acid in a different, aligned IgG isotype. For example,

because IgG1 comprises a tyrosine and IgG2 comprises a phenylalanine at EU position 296, a F296Y substitution in IgG2 is considered an IgG subclass modification. Similarly, because IgG1 has a proline at position 241 and IgG4 has a serine, an IgG4 molecule with a S241P is considered an IgG subclass modification. Note that subclass modifications are considered amino acid substitutions herein.

[00133] By "amino acid" and "amino acid identity" as used herein is meant one of the 20 naturally occurring amino acids that are coded for by DNA and RNA.

[00134] By "effector function" as used herein is meant a biochemical event that results from the interaction of an antibody Fc region with an Fc receptor or ligand. Effector functions include but are not limited to antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC). In many cases, it is desirable to ablate most or all effector functions using either different IgG isotypes (*e.g.* IgG4) or amino acid substitutions in the Fc domain; however, preserving binding to the FcRn receptor is desirable, as this contributes to the half-life of the fusion protein in human serum.

[00135] By "FcRn" or "neonatal Fc Receptor" as used herein is meant a protein that binds the IgG antibody Fc region and is encoded at least in part by an FcRn gene.

[00136] By "target cell" as used herein is meant a cell that expresses a target polypeptide or protein.

[00137] By "host cell" in the context of producing the variant sBCMA or the sBCMA variant – Fc fusion proteins according to the invention herein is meant a cell that contains the exogenous nucleic acids encoding the components of the variant sBCMA or the sBCMA variant – Fc fusion protein, and is capable of expressing such variant sBCMA or Fc fusion protein under suitable conditions. Suitable host cells are described below.

[00138] By "improved activity" or "improved function" herein meant a desirable change of at least one biochemical property. An improved function in this context can be measured as a percentage increase or decrease of a particular activity, or as a "fold" change, with increases of desirable properties (*e.g.* increased binding affinity and/or specificity for APRIL and/or BAFF, increased protein stability of the, increased half-life *in vivo*, *etc.*). In general, percentage changes are used to describe changes in biochemical activity of less than

100%, and fold-changes are used to describe changes in biochemical activity of greater than 100% (as compared to the parent protein). In the present invention, percentage changes (usually increases) of biochemical activity of at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 98% and 99% can be accomplished. In the present invention, a "fold increase" (or decrease) is measured as compared to the parent protein. In many embodiments, the improvement is at least 1.4 fold, 1.5 fold, 1.6 fold, 1.8 fold, 2 fold, 3 fold, 4 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 50 fold, 100 fold, 200 fold or higher.

C. sBCMA Variant – Fc Fusion Proteins

[00139] The sBCMA variant – Fc fusion proteins of the present invention include a composition comprising a variant sBCMA domain, an Fc domain, and optionally a linker linking the variant sBCMA domain with the Fc domain.

[00140] In some embodiments, the present invention provides the composition as described herein, wherein said fusion protein comprises, from N- to C-terminal:

a) said variant sBCMA domain;

b) said optional linker; and

c) said Fc domain.

[00141] In some embodiments, the present invention provides the composition as described herein, wherein said fusion protein comprises, from N- to C-terminal:

a) said Fc domain;

b) said optional linker; and

c) said variant sBCMA domain.

D. Variant sBCMA Proteins and Domains

[00142] The invention provides variant sBCMA proteins both independently and as fusion protein constructs as an sBCMA domain fused with Fc domains. Variant sBCMA proteins of the present invention include at least a portion of the soluble ECD of human BCMA, generally the entire ECD domain (SEQ ID NO:1) as shown in Figure 30, with

amino acid variants. In some embodiments, variant sBCMA proteins or sBCMA variants exhibits increased binding affinity and/or specificity for APRIL and/or BAFF as compared to wild-type sBCMA as determined by binding affinity assays in the art and discussed below, such as Biacore or Octet assays.

[00143] In some embodiments, variant sBCMA proteins (either as isolated proteins or as sBCMA domains of the fusion proteins herein) are antagonists that bind to APRIL and/or BAFF to mitigate or to block their interaction with endogenous BCMA, BAFFR, and TACI receptors. Variant sBCMA proteins as antagonists can be used in treating conditions associated with altered signaling pathways through BCMA, BAFFR, TACI and/or other receptors that are activated through binding to APRIL and/or BAFF, in particular tumor therapy/chemotherapy, immunomodulatory and/or fibrotic diseases.

[00144] In an additional embodiment, variant sBCMA proteins (either as isolated proteins or as sBCMA domains of the fusion proteins herein) can be used in a method of inhibiting the activity of APRIL in a subject having an autoimmune disease that expresses APRIL, said method comprising administering to the subject a therapeutically effective dose of one or more said variant sBCMA proteins as disclosed herein.

[00145] In an additional embodiment, variant sBCMA proteins (either as isolated proteins or as sBCMA domains of the fusion proteins herein) can be used in a method of inhibiting the activity of APRIL in a subject having an autoimmune disease that expresses BCMA, TACI and/or other receptors that are activated through binding to APRIL, said method comprising administering to the subject a therapeutically effective dose of one or more said variant sBCMA proteins as disclosed herein.

[00146] In a further embodiment, variant sBCMA proteins (either as isolated proteins or as sBCMA domains of the fusion proteins herein) can be used in a method of inhibiting the activity of APRIL in a subject having fibrosis that expresses APRIL, said method comprising administering to the subject a therapeutically effective dose of one or more said variant sBCMA proteins as disclosed herein.

[00147] In a further embodiment, variant sBCMA proteins (either as isolated proteins or as sBCMA domains of the fusion proteins herein) can be used in a method of inhibiting the activity of APRIL in a subject having fibrosis that expresses BCMA, TACI and/or other

receptors that are activated through binding to APRIL, said method comprising administering to the subject a therapeutically effective dose of one or more said variant sBCMA proteins as disclosed herein.

[00148] In an additional embodiment, variant sBCMA proteins (either as isolated proteins or as sBCMA domains of the fusion proteins herein) can be used in a method of inhibiting B-cell growth, immunoglobulin production, or both in a subject, where the variant sBCMA protein binds to BAFF, said method comprising administering to the subject a therapeutically effective dose of one or more said variant sBCMA proteins as disclosed herein.

[00149] In a further embodiment, variant sBCMA proteins (either as isolated proteins or as sBCMA domains of the fusion proteins herein) can be used in a method of inhibiting the activity of BAFF in a subject having B cell hyperplasia or an autoimmune disease expressing BCMA, BAFFR, TACI and/or other receptors that are activated through binding to BAFF, said method comprising administering to the subject a therapeutically effective dose of one or more said variant sBCMA proteins as disclosed herein.

[00150] In an additional embodiment, variant sBCMA proteins (either as isolated proteins or as sBCMA domains of the fusion proteins herein) can be used in a method of treating an autoimmune disease expressing at least one receptor selected from the group consisting of BCMA, BAFFR, TACI and other receptor(s) that are activated through binding to BAFF in a subject, said method comprising administering to the subject a therapeutically effective dose of one or more said variant sBCMA proteins as disclosed herein.

[00151] In a further embodiment, variant sBCMA proteins (either as isolated proteins or as sBCMA domains of the fusion proteins herein) can be used in a method of treating an autoimmune disease expressing BAFF and/or APRIL in a subject, said method comprising administering to the subject a therapeutically effective dose of one or more said variant sBCMA proteins as disclosed herein.

[00152] In an additional embodiment, variant sBCMA proteins (either as isolated proteins or as sBCMA domains of the fusion proteins herein) can be used in a method of treating fibrosis expressing BCMA, BAFFR and/or TACI in a subject, said method

comprising administering to the subject a therapeutically effective dose of one or more said variant sBCMA proteins as disclosed herein.

[00153] In an additional embodiment, variant sBCMA proteins (either as isolated proteins or as sBCMA domains of the fusion proteins herein) can be used in a method of treating fibrosis expressing BAFF and/or APRIL in a subject, said method comprising administering to the subject a therapeutically effective dose of one or more said variant sBCMA proteins as disclosed herein.

[00154] In some embodiments, variant sBCMA proteins include amino acid substitutions, deletions or insertions or any combination thereof as compared to the wild type sBCMA, and increase their binding activity to either APRIL, BAFF or both as compared to the wild-type sBCMA.

[00155] The present disclosure provides variant sBCMA protein(s) comprising at least one amino acid substitution at one or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9 or 10) positions as compared to a parent sBCMA. In some embodiments, a variant sBCMA has at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, but less than 100% sequence identity to the parent sBCMA. In some embodiments, a parent sBCMA domain is human wild-type sBCMA. In some embodiments, a parent sBCMA domain has the amino acid sequence of SEQ ID NO:1. In some embodiments, a variant sBCMA has 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%, but less than 100% sequence identity to SEQ ID NO:1. In some embodiments, as noted herein, a variant sBCMA can have N-terminal and/or C terminal truncations compared to wild type sBCMA as long as the truncated variant sBCMA retains biological activity (*e.g.* binding to APRIL and/or BAFF), as measured by one of the binding assays outlined herein. To be clear, the variant BCMA of the present invention has at least one amino acid substitution as compared to SEQ ID NO:1, and thus is not SEQ ID NO:1.

[00156] In some embodiments, a variant sBCMA described herein has a binding affinity for TGF family member (i.e., APRIL and/or BAFF) that is stronger than the wild-type sBCMA polypeptide/domain. In some embodiments, the variant sBCMA has a binding affinity for APRIL and/or BAFF that is at least 1.4-fold, 1.5-fold, 1.6-fold, 1.8-fold, 2-fold,

3-fold, 4-fold, 5-fold, 10-fold, 50-fold, 100-fold, 200-fold or greater than that of the wild-type sBCMA.

[00157] In certain embodiments, the binding affinity of the variant sBCMA for APRIL and/or BAFF is increased by at least about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50% or higher as compared to that of the wild-type sBCMA. In other embodiments, the variant sBCMA proteins of the present invention have a Kd value of less than about 1×10^{-8} M, 1×10^{-9} M, 1×10^{-10} M, 1×10^{-12} M or 1×10^{-15} M for binding with APRIL and/or BAFF. In yet other embodiments, sBCMA variants inhibit or compete with wild-type sBCMA in binding to APRIL and/or BAFF either *in vivo*, *in vitro* or both.

1. Specific Variant sBCMA Proteins

[00158] The present invention provides a composition comprising a variant sBCMA comprising at least one amino acid substitution as compared to SEQ ID NO:1, wherein said amino acid substitution is at a position number selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 14, 16, 19, 20, 22, 23, 25, 26, 29, 31, 32, 35, 36, 38, 39, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, and 54, wherein the numbering is according to the EU index.

[00159] In some embodiments, the variant sBCMA as described herein has at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO:1.

[00160] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the methionine at position 1 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing proline (due to steric effects). In some embodiments, the amino acid substitution is selected from M1A, M1C, M1I, M1R, M1T, and M1V.

[00161] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the leucine at position 2 with the position numbering starting from

the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing proline (due to steric effects). In some embodiments, the amino acid substitution is L2C or L2S.

[00162] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the glutamine at position 3 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation). In some embodiments, the amino acid substitution is Q3P or Q3R.

[00163] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the methionine at position 4 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is selected from M4E, M4I, M4T, and M4V.

[00164] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the alanine at position 5 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is A5T.

[00165] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the glycine at position 6 with the position numbering starting from

the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is G6E.

[00166] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the glutamine at position 7 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is Q7R.

[00167] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the serine at position 9 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, threonine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation). In some embodiments, the amino acid substitution is selected from S9A, S9F and S9P.

[00168] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the glutamine at position 10 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation). In some embodiments, the amino acid substitution is selected from Q10H, Q10P and Q10R.

[00169] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the asparagine at position 11 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is N11D or N11S.

[00170] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the glutamic acid at position 12 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is E12K.

[00171] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the phenylalanine at position 14 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is F14L.

[00172] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the serine at position 16 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, threonine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine

(due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is selected from S16G, S16N, and S16R.

[00173] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the histidine at position 19 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is H19L or H19Y.

[00174] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the alanine at position 20 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is A20Vor A20T.

[00175] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the isoleucine at position 22 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is I22M or I22V.

[00176] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the proline at position 23 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine,

methionine, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is P23S.

[00177] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the glutamine at position 25 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is Q25R.

[00178] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the leucine at position 26 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is L26F.

[00179] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the serine at position 29 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, threonine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is S29A.

[00180] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the asparagine at position 31 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, glutamic acid, glutamine, aspartic acid,

lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is N31D or N31S.

[00181] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the threonine at position 32 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation). In some embodiments, the amino acid substitution is selected from T32A, T32I and T32P.

[00182] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the leucine at position 35 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation). In some embodiments, the amino acid substitution is L35S or L35P.

[00183] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the threonine at position 36 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation). In some embodiments, the amino acid substitution is selected from T36A, T36I, and T36P.

[00184] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the glutamine at position 38 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19

naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is Q38R.

[00185] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the arginine at position 39 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is R39H.

[00186] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the asparagine at position 42 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is selected from N42D, N42R and N42S.

[00187] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the alanine at position 43 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is A43T or A43V.

[00188] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the serine at position 44 with the position numbering starting from

the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, threonine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is selected from S44D, S44G, S44N and S44R.

[00189] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the valine at position 45 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is V45A or V45M.

[00190] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the threonine at position 46 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is T46A or T46I.

[00191] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the asparagine at position 47 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is selected from N47D, N47K, N47R and N47S.

[00192] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the serine at position 48 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, threonine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation). In some embodiments, the amino acid substitution is selected from S48L, S48P and S48T.

[00193] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the valine at position 49 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is V49A or V49M.

[00194] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the lysine at position 50 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, glutamine, aspartic acid, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is selected from K50E, K50G, K50R and K50T.

[00195] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the glycine at position 51 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing

cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is G51E.

[00196] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the threonine at position 52 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is T52A or T52M.

[00197] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the asparagine at position 53 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, alanine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is selected from N53D, N53K and N53S.

[00198] In some embodiments, the variant sBCMA as described herein comprises an amino acid substitution of the alanine at position 54 with the position numbering starting from the mature region. In some embodiments, the substitution is with any other of the 19 naturally occurring amino acids, serine, threonine, asparagine, glutamic acid, glutamine, aspartic acid, lysine, arginine, histidine, cysteine, glycine, isoleucine, leucine, methionine, proline, phenylalanine, tryptophan, valine and tyrosine, with some embodiments not utilizing cysteine (due to possible disulfide formation) or proline (due to steric effects). In some embodiments, the amino acid substitution is A54V or A54T.

[00199] In some embodiments, the variant sBCMA as described herein comprises amino acid substitution(s) selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16G, S16N, S16R, H19L, H19Y, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P,

L35S, L35P, T36A, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

[00200] In some embodiments, the variant sBCMA as described herein comprises amino acid substitution(s) selected from the group consisting of M1V, L2S, Q3P, M4T, S9P, N11D, S16G, H19Y, N31S, N31D, T32I, T36A, R39H, N47S, K50E, and N53E.

[00201] In some embodiments, the variant sBCMA as described herein comprises amino acid substitution(s) selected from the group consisting of S16G, H19Y and T36A.

[00202] In some embodiments, the variant sBCMA as described herein comprises amino acid substitutions selected from the group consisting of L2S/S9P/E12K/N31D/T36A/N42S/N53S, M1V/T32P/T36A/T46I/N53D/A54V, Q3R/S16N/T36A/A43T, F14L/S16G/T36A/V45A/N47D, M1T/M4V/S9F/S16G/T32A/Q38R, M1A/S9A/Q38R, G6E/Q25R/Q38R, M1V/M4I/G6E/S9P/N11D/V49M/T52M/A54V, N11D/S16G/N31S, N11D/H19Y/I22M/T32P/N47S/N53S, G6E/Q7R/H19Y/L35S, H19Y/N42D/S48P/T52A, M1V/N31D/T32I/T36A, M1V/A5T/H19L/T36A, M1T/N31D/T32A/T36A/Q38R/S44D/V49A/K50E, M1V/T36A/Q38R/A43V, M1V/L2S/S9P/Q10H/T36A/Q38R/K50G, T36A/Q38R/N53S, M1T/L2S/L35P/T36A/Q38R/T46A/K50R, A5T/A20V/T36A/Q38R, M1T/S16G/I22V/T36A/S44G/T46A/V49A, S16G/T36A, M1I/N11D/S16G/I22M/S29A/T36A/S44G/K50R, M1C/L2C/Q3R/M4E/N11D/S16G/T36P, M1I/N11D/S16G/I22M/S29A/T36A/S44G/K50R, N11D/N31D/T32I/T36A/S44N/N47D/N53D, M1R/L2C/Q3R, H19Y/T36A/S44G, H19Y/T32I/T36A/V49A, H19Y/N31S/T36A/V45A, H19Y/N31S/T36A, H19Y/T36P/T52A, H19Y/N31D/T52M, M1V/H19Y/V45M, S16G/H19Y/N47D, S16G/H19Y/K50T, S16G/H19Y/S44N/K50R, N11D/H19Y/S48T, S9P/N11D/S16R/T32A/Q38R/S44G/T46I/T52A/N53D/A54T, N11D/S16G/S44R, H19L/T32A/S44G/G51E/T52A, S16N/H19Y/T36A/K50R, M1V/H19Y/T36A/R39H/T46A, M1V/H19Y/T36A, H19Y/T36A/N42D/N47S/S48P, M1V/H19Y/T36A/S44G/N47D, M1V/H19Y/T36A/N42R/N53S, H19Y/L35P/T36A/N42D/T46I/V49A,

Q3P/S9P/H19Y/N31S/T36A/R39H/N47R/K50E, M1V/H19Y/T36A/N42R/N53S, M1T/H19Y/T36A, M1V/S16N/H19Y/I22M/T36A, M1T/N11D/H19Y/T36A/N42S/V45A/N53S, N11D/S16G/H19Y/T36A/N47S/N53D, M1V/S9P/Q10P/S16G/H19Y/L26F/T36A/A43V/N53D, S16G/H19Y/T36A/V49A/N53D, S16G/T36A/A43T/S44G/V45M, M4V/S9P/S16G/T36A/Q38R, S9P/N11S/S16G/T36A/Q38R, N11D/E12K/S16R/T36A/T52M, M4V/T32I/T36A/Q38R/A43T/V45A/S48P, S9P/N11D/S16G/Q25R, M1T/A5T/S9P/S16G/Q25R/N31D/V49M, L2S/S9P/S16G/A20T/T32I/Q38R/N42D/T46A/S48L, S16G/Q25R/T46A, G6E/S9A/S16G/Q25R/N31D/N47S/T52M, H19Y/Q38R/T52M, N11D/H19Y/I22M/T32P/N47S/N53S, S16G/H19Y/T36A, S16G/H19Y/T36A/N53D, S9P/N11D/S16G/H19Y/T36A/N47S/N53D, Q3P/S9P/H19Y/N31S/T36A/R39H/N47R/K50E, M1V/L2S/M4T/N11D/H19Y/T36A, M1V/L2S/M4T/N11D/T36A, M1V/L2S/M4T/H19Y/T36I/V45A/V49M, M1V/L2S/M4T/N11D/H19Y/T36A, M1V/L2S/M4T/S9P/Q10R/H19Y/T36A/T46A/N47S, M1V/L2S/M4T/S16G/N31D/T32I/T36A, M1V/M4T/T36A/Q38R/N53K, M1T/N11D/H19Y/T36A/N42S/V45A/N53S, M1T/N31D/T32A/T36A/A38R/S44D/V49A/K50E, M1T/S9P/P23S/Q38R/N42S/S48P/V49A/A54V, H19Y/T36A/S44G, H19Y/T36A, and M4T/T36A/Q38R/N42S/S44G/T46A/N47K/S48P/T52A.

[00203] In some embodiments, the variant sBCMA as described herein comprises amino acid substitutions S16G/H19Y/T36A, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

[00204] In some embodiments, the variant sBCMA as described herein comprises amino acid substitutions S16G/H19Y/T36A/N53D, and at least one further amino acid

substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53K, N53S, A54V, and A54T.

[00205] In some embodiments, the variant sBCMA as described herein comprises amino acid substitutions S9P/N11D/S16G/H19Y/T36A/N47S/N53D, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, Q10H, Q10P, Q10R, N11S, E12K, F14L, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53K, N53S, A54V, and A54T.

[00206] In some embodiments, the variant sBCMA as described herein comprises amino acid substitutions Q3P/S9P/H19Y/N31S/T36A/R39H/N47R/K50E, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16G, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47S, S48L, S48P, S48T, V49A, V49M, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

[00207] In some embodiments, the variant sBCMA as described herein comprises amino acid substitutions M1V/L2S/M4T/S16G/N31D/T32I/T36A, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, L2C, Q3P, Q3R, M4E, M4I, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16N, S16R, H19L, H19Y, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31S, T32A, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D,

N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

[00208] In some embodiments, the variant sBCMA as described herein has at least 90% sequence identity to SEQ ID NO: 67.

[00209] In some embodiments, the variant sBCMA as described herein has at least 90% sequence identity to SEQ ID NO: 68.

[00210] In some embodiments, the variant sBCMA as described herein has at least 90% sequence identity to SEQ ID NO: 69.

[00211] In some embodiments, the variant sBCMA as described herein has at least 90% sequence identity to SEQ ID NO: 49.

[00212] In some embodiments, the variant sBCMA as described herein has at least 90% sequence identity to SEQ ID NO: 74.

[00213] In some embodiments, the variant sBCMA as described herein has the amino acid sequence of SEQ ID NO: 67.

[00214] In some embodiments, the variant sBCMA as described herein has the amino acid sequence of SEQ ID NO: 68.

[00215] In some embodiments, the variant sBCMA as described herein has the amino acid sequence of SEQ ID NO: 69.

[00216] In some embodiments, the variant sBCMA as described herein has the amino acid sequence of SEQ ID NO: 49.

[00217] In some embodiments, the variant sBCMA as described herein has the amino acid sequence of SEQ ID NO: 74.

[00218] The clone Nos., amino acid substitutions as compared to the amino acid sequence of SEQ ID NO:1, and assigned SEQ ID NOs of exemplary variant sBCMA proteins are shown in Table 2.

[00219] **Table 2**: The clone numbers, amino acid substitutions as compared to the amino acid sequence of SEQ ID NO:1, and the assigned SEQ ID NOs. of exemplary variant sBCMA proteins/domains.

Clone Nos.	**Amino Acid Substitutions as compared to SEQ ID NO:1**	**SEQ ID Nos.**
# 1	L2S/S9P/E12K/N31D/T36A/N42S/N53S	SEQ ID NO: 2
# 2	M1V/T32P/T36A/T46I/N53D/A54V	SEQ ID NO: 3
# 3	Q3R/S16N/T36A/A43T	SEQ ID NO: 4
# 4	F14L/S16G/T36A/V45A/N47D	SEQ ID NO: 5
# 5	M1T/M4V/S9F/S16G/T32A/Q38R	SEQ ID NO: 6
# 6	M1A/S9A/Q38R	SEQ ID NO: 7
# 7	G6E/Q25R/Q38R	SEQ ID NO: 8
# 8	M1V/M4I/G6E/S9P/N11D/V49M/T52M/A54V	SEQ ID NO: 9
# 9	N11D/S16G/N31S	SEQ ID NO: 10
# 10 and 70	N11D/H19Y/I22M/T32P/N47S/N53S	SEQ ID NO: 11
# 11	G6E/Q7R/H19Y/L35S	SEQ ID NO: 12
# 12	H19Y/N42D/S48P/T52A	SEQ ID NO: 13
# 13	M1V/N31D/T32I/T36A	SEQ ID NO: 14
# 14	M1V/A5T/H19L/T36A	SEQ ID NO: 15

# 15	M1T/N31D/T32A/T36A/Q38R/S44D/V49A/K50E	SEQ ID NO: 16
# 16	M1V/T36A/Q38R/A43V	SEQ ID NO: 17
# 17	M1V/L2S/S9P/Q10H/T36A/Q38R/K50G	SEQ ID NO: 18
# 18	T36A/Q38R/N53S	SEQ ID NO: 19
# 19	M1T/L2S/L35P/T36A/Q38R/T46A/K50R	SEQ ID NO: 20
# 20	A5T/A20V/T36A/Q38R	SEQ ID NO: 21
# 21	M1T/S16G/I22V/T36A/S44G/T46A/V49A	SEQ ID NO: 22
# 22 & 73	S16G/T36A	SEQ ID NO: 23
# 23 and 25	M1I/N11D/S16G/I22M/S29A/T36A/S44G/K50R	SEQ ID NO: 24
# 24	M1C/L2C/Q3R/M4E/N11D/S16G/T36P	SEQ ID NO: 25
# 26	N11D/N31D/T32I/T36A/S44N/N47D/N53D	SEQ ID NO: 26
# 27	M1R/L2C/Q3R/N11D/H19Y/T36A/N42S/V45A/N53S	SEQ ID NO: 27
# 28 and 116	H19Y/T36A/S44G	SEQ ID NO: 28
# 29	H19Y/T32I/T36A/V49A	SEQ ID NO: 29
# 30	H19Y/N31S/T36A/V45A	SEQ ID NO: 30
# 31	H19Y/N31S/T36A	SEQ ID NO: 31
# 32	H19Y/T36P/T52A	SEQ ID NO: 32

# 33	H19Y/N31D/T52M	SEQ ID NO: 33
# 34	M1V/H19Y/V45M	SEQ ID NO: 34
# 35	S16G/H19Y/N47D	SEQ ID NO: 35
# 36	S16G/H19Y/K50T	SEQ ID NO: 36
# 37	S16G/H19Y/S44N/K50R	SEQ ID NO: 37
# 38	N11D/H19Y/S48T	SEQ ID NO: 38
# 39	S9P/N11D/S16R/T32A/Q38R/S44G/T46I/T52A/N53D/A54T	SEQ ID NO: 39
# 40	N11D/S16G/S44R	SEQ ID NO: 40
# 41	H19L/T32A/S44G/G51E/T52A	SEQ ID NO: 41
# 42	S16N/H19Y/T36A/K50R	SEQ ID NO: 42
# 43	M1V/H19Y/T36A/R39H/T46A	SEQ ID NO: 43
# 44	M1V/H19Y/T36A	SEQ ID NO: 44
# 45	H19Y/T36A/N42D/N47S/S48P	SEQ ID NO: 45
# 46	M1V/H19Y/T36A/S44G/N47D	SEQ ID NO: 46
# 47 and 50	M1V/H19Y/T36A/N42R/N53S	SEQ ID NO: 47
# 48	H19Y/L35P/T36A/N42D/T46I/V49A	SEQ ID NO: 48
# 49, 75-94	Q3P/S9P/H19Y/N31S/T36A/R39H/N47R/K50E	SEQ ID NO: 49

# 51	M1T/H19Y/T36A	SEQ ID NO: 50
# 52	M1V/S16N/H19Y/I22M/T36A	SEQ ID NO: 51
# 53, 54 and 113	M1T/N11D/H19Y/T36A/N42S/V45A/N53S	SEQ ID NO: 52
# 55 and 56	N11D/S16G/H19Y/T36A/N47S/N53D	SEQ ID NO: 53
# 57	M1V/S9P/Q10P/S16G/H19Y/L26F/T36A/A43V/N53D	SEQ ID NO: 54
# 58	S16G/H19Y/T36A/V49A/N53D	SEQ ID NO: 55
# 59	S16G/T36A/A43T/S44G/V45M	SEQ ID NO: 56
# 60	M4V/S9P/S16G/T36A/Q38R	SEQ ID NO: 57
# 61	S9P/N11S/S16G/T36A/Q38R	SEQ ID NO: 58
# 62	N11D/E12K/S16R/T36A/T52M	SEQ ID NO: 59
# 63	M4V/T32I/T36A/Q38R/A43T/V45A/S48P	SEQ ID NO: 60
# 64	S9P/N11D/S16G/Q25R	SEQ ID NO: 61
# 65	M1T/A5T/S9P/S16G/Q25R/N31D/V49M	SEQ ID NO: 62
# 66	L2S/S9P/S16G/A20T/T32I/Q38R/N42D/T46A/S48L	SEQ ID NO: 63
# 67	S16G/Q25R/T46A	SEQ ID NO: 64
# 68	G6E/S9A/S16G/Q25R/N31D/N47S/T52M	SEQ ID NO: 65
# 69	H19Y/Q38R/T52M	SEQ ID NO: 66

# 71	S16G/H19Y/T36A/N53D	SEQ ID NO: 67
# 72	S16G/H19Y/T36A	SEQ ID NO: 68
# 74	S9P/N11D/S16G/H19Y/T36A/N47S/N53D	SEQ ID NO: 69
# 95, and 101 -103	M1V/L2S/M4T/N11D/H19Y/T36A	SEQ ID NO: 70
# 96 -99	M1V/L2S/M4T/N11D/T36A	SEQ ID NO: 71
# 100	M1V/L2S/M4T/H19Y/T36I/V45A/V49M	SEQ ID NO: 72
# 104 and 105	M1V/L2S/M4T/S9P/Q10R/H19Y/T36A/T46A/N47S	SEQ ID NO: 73
# 106 - 111	M1V/L2S/M4T/S16G/N31D/T32I/T36A	SEQ ID NO: 74
# 112	M1V/M4T/T36A/Q38R/N53K	SEQ ID NO: 75
# 114	M1T/N31D/T32A/T36A/A38R/S44D/V49A/K50E	SEQ ID NO: 76
# 115	M1T/S9P/P23S/Q38R/N42S/S48P/V49A/A54V	SEQ ID NO: 77
# 117	H19Y/T36A	SEQ ID NO: 78
# 118	M4T/T36A/Q38R/N42S/S44G/T46A/N47K/S48P/T52A	SEQ ID NO: 79

[00220] In some embodiments, the variant sBCMA as described herein exhibits enhanced binding affinity for APRIL or BAFF as compared to SEQ ID NO:1.

[00221] In some embodiments, the variant sBCMA as described herein exhibits enhanced binding affinity for APRIL and BAFF as compared to SEQ ID NO:1.

[00222] In some embodiments, the sBCMA variant – Fc fusion protein as described herein has the amino acid sequence of SEQ ID NO:80.

[00223] In some embodiments, the sBCMA variant – Fc fusion protein as described herein has the amino acid sequence of SEQ ID NO:81.

[00224] In some embodiments, the sBCMA variant – Fc fusion protein as described herein has the amino acid sequence of SEQ ID NO:82.

[00225] In some embodiments, the sBCMA variant – Fc fusion protein as described herein has the amino acid sequence of SEQ ID NO:83.

[00226] In some embodiments, the sBCMA variant – Fc fusion protein as described herein has the amino acid sequence of SEQ ID NO:84.

2. Assays to Measure Binding Affinity

[00227] As outlined herein, the present invention provides sBCMA variants and fusion proteins comprising these variants that exhibit increased binding affinity for either or both of human APRIL and/or human BAFF. In this context, increased binding affinity is compared to the human wild type BCMA or SEQ ID NO:1 *in vitro* or *ex vivo* studies as outlined below. In some embodiments, the variant sBCMA domain as described herein has a binding affinity for TGF family member (e.g., APRIL and/or BAFF) that is stronger than the wild-type sBCMA polypeptide/domain and/or SEQ ID NO:1. In some embodiments, the variant sBCMA domain has a binding affinity for APRIL and/or BAFF that is at least 1.4-fold, 1.5-fold, 1.6-fold, 1.7-fold, 1.8-fold, 1.9-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, 50-fold, 100-fold, 200-fold or greater than that of the wild-type sBCMA and/or SEQ ID NO:1.

[00228] The ability of an sBCMA variant to bind to APRIL and/or BAFF can be determined, for example, by the ability of the putative ligand to bind to APRIL and/or BAFF coated on an assay plate. Alternatively, binding affinity of an sBCMA (variant) for APRIL and/or BAFF can be determined by displaying the sBCMA (variant) on a microbial cell surface, *e.g.*, a yeast cell surface and detecting the bound complex by, for example, flow cytometry *(see*, Example 3). The binding affinity of sBCMA (variant) for APRIL and/or BAFF can be measured using any appropriate method as would be understood by those skilled in the art including, but not limited to, radioactive ligand binding assays, non-radioactive (fluorescent) ligand binding assays, surface plasmon resonance (SPR), such as

Biacore™, Octet™, plasmon-waveguide resonance (PWR), thermodynamic binding assays, whole cell ligand-binding assays, and structure-based ligand binding assays.

3. Formats of the Fusion Proteins

[00229] As described herein, the format of the fusion protein can take on several configurations, with the component domains switching order in the protein (from N- to C-terminal). In one embodiment, a fusion protein comprises, from N- to C-terminus, a variant sBCMA domain-domain linker-Fc domain. In some embodiments, a fusion protein comprises, from N- to C-terminus, Fc domain-domain linker- variant sBCMA domain. In some embodiments, a linker is not used, in which case the fusion protein comprises from N- to C-terminus, either variant sBCMA domain-Fc domain or Fc domain- variant sBCMA domain. Note that in some cases, the same fusion protein can be labeled somewhat differently. For example, in the case in which the Fc domain includes a hinge domain, a fusion protein comprising variant sBCMA domain-Fc domain still includes a linker in the form of the hinge domain. Alternatively, this same protein may not have the hinge domain included in the Fc domain, in which case the fusion protein comprises variant sBCMA domain-CH2-CH3.

[00230] Thus, in some embodiments, the present disclosure provides a variant sBCMA – Fc fusion protein as described herein, where the Fc domain comprises a hinge domain and the variant sBCMA domain is linked with the Fc domain by the hinge domain: variant sBCMA domain-hinge domain-CH2-CH3.

[00231] In some embodiments, the present disclosure provides a variant sBCMA – Fc fusion proteins as described above, where the Fc domain comprises a hinge domain and the variant sBCMA domain is linked with the Fc domain by an additional linker as described herein. That is, the fusion protein can be, from N- to C-terminal: variant sBCMA domain-domain linker-hinge domain-CH2-CH3; variant sBCMA domain-domain linker-CH2-CH3; hinge domain-CH2-CH3-domain linker-variant sBCMA domain or CH2-CH3-domain linker-variant sBCMA domain.

[00232] In some embodiments, the present disclosure provides variant sBCMA – Fc fusion proteins as described above, where the Fc domain does not comprise a hinge domain

and the variant sBCMA domain is linked with the Fc domain by a domain linker (*e.g.* non-hinge) as described herein.

[00233] In some embodiments, the present disclosure provides a composition comprising an sBCMA variant – Fc fusion protein comprising:

a) a variant sBCMA domain comprising at least one amino acid substitution as compared to SEQ ID NO:1, wherein said amino acid substitution is at a position number selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 14, 16, 19, 20, 22, 23, 25, 26, 29, 31, 32, 35, 36, 38, 39, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, and 54, wherein the numbering is according to the EU index;

b) an optional linker; and

c) an Fc domain.

[00234] In some embodiments, the sBCMA variant – Fc fusion protein as described herein comprises, from N- to C-terminal:

a) said variant sBCMA domain;

b) said optional linker; and

c) said Fc domain.

[00235] In some embodiments, the sBCMA variant – Fc fusion protein as described herein comprises, from N- to C-terminal:

a) said Fc domain;

b) said optional linker; and

c) said variant sBCMA domain.

[00236] In some embodiments, a variant sBCMA domain of the sBCMA variant – Fc fusion protein as described herein serves to increase the binding affinity for APRIL and/or BAFF. In various embodiments, a (variant) Fc domain of the sBCMA variant – Fc fusion protein as described herein increases the half-life of the fusion protein. In a number of embodiments, fusion proteins are used to treat fibrosis and/or immunomodulatory diseases.

[00237] The names of the designated proteins/protein domains and corresponding amino acid sequences are listed in Table 3, respectively.

Table 3. SEQ ID numbers, descriptions and corresponding amino acid sequences.

SEQ ID NO (Description)	**Amino Acid Sequence**
SEQ ID NO:1 (sBCMA WT ECD)	MLQMAGQCSQNEYFDSLLHACIPCQLRCSSNTPPLTCQRY CNASVTNSVKGTNA
SEQ ID NO:87 (domain linker)	IEGRMD
SEQ ID NO:88 (domain linker)	GGGGS

[00238] In some embodiments, the variant sBCMA domain as described herein includes amino acid substitution(s), deletion(s) or insertion(s) or any combination thereof to the amino acid sequence of SEQ ID NO:1 that increases its binding activity to either APRIL, BAFF or both as compared to wild-type sBCMA.

[00239] The present disclosure provides variant sBCMA domains comprising at least one amino acid substitution at one or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9 or 10) positions as compared to the amino acid sequence of SEQ ID NO:1. In some embodiments, the variant sBCMA domain has at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, but less than 100% sequence identity to the parent sBCMA domain. In some embodiments, a parent sBCMA domain has the amino acid sequence of SEQ ID NO:1. In some embodiments, a variant sBCMA domain has 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%, but less than 100% sequence identity to SEQ ID NO:1. In some embodiments, as noted herein, a variant sBCMA domain can have N-terminal and/or C terminal truncations compared to wild type sBCMA as long as the truncated variant sBCMA retains biological activity (*e.g.* binding to APRIL and/or BAFF), as measured by one of the binding assays outlined herein. To be clear, the variant BCMA domain of the present invention has at least one amino acid substitution and thus is not the amino acid sequence of SEQ ID NO:1.

[00240] In some embodiments, the variant sBCMA domain as described herein has amino acid substitution(s) at one position, two positions, three positions, four positions, five positions, six positions, seven positions, eight positions, nine positions, or ten positions.

[00241] In certain embodiments, the binding affinity of the variant sBCMA domain as described herein for APRIL and/or BAFF is increased by at least about 0.4%, 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50% or higher as compared to that of the wild-type sBCMA. In other embodiments, variant BCMA domains of the present invention have a binding affinity of less than about 1×10^{-8} M, 1×10^{-9} M, 1×10^{-10} M, 1×10^{-12} M or 1×10^{-15} M for APRIL and/or BAFF. In yet other embodiments, variant BCMA domains as described herein inhibit or compete with wild-type sBCMA binding to APRIL and/or BAFF either *in vivo*, *in vitro* or both.

[00242] In some embodiments, the variant sBCMA domain as described herein comprises at least one amino acid substitution as compared to SEQ ID NO:1, wherein said amino acid substitution is at a position number selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 14, 16, 19, 20, 22, 23, 25, 26, 29, 31, 32, 35, 36, 38, 39, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, and 54, wherein the numbering is according to the EU index.

[00243] In some embodiments, the variant sBCMA domain as described herein has at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO:1.

[00244] In some embodiments, the variant sBCMA domain as described herein comprises amino acid substitution(s) selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16G, S16N, S16R, H19L, H19Y, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36A, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

[00245] In some embodiments, the variant sBCMA domain as described herein comprises amino acid substitution(s) selected from the group consisting of M1V, L2S, Q3P, M4T, S9P, N11D, S16G, H19Y, N31S, N31D, T32I, T36A, R39H, N47S, K50E, and N53E.

[00246] In some embodiments, the variant sBCMA domain as described herein comprises amino acid substitution(s) selected from the group consisting of S16G, H19Y and T36A.

[00247] In some embodiments, the variant sBCMA domain as described herein comprises amino acid substitutions selected from the group consisting of L2S/S9P/E12K/N31D/T36A/N42S/N53S, M1V/T32P/T36A/T46I/N53D/A54V, Q3R/S16N/T36A/A43T, F14L/S16G/T36A/V45A/N47D, M1T/M4V/S9F/S16G/T32A/Q38R, M1A/S9A/Q38R, G6E/Q25R/Q38R, M1V/M4I/G6E/S9P/N11D/V49M/T52M/A54V, N11D/S16G/N31S, N11D/H19Y/I22M/T32P/N47S/N53S, G6E/Q7R/H19Y/L35S, H19Y/N42D/S48P/T52A, M1V/N31D/T32I/T36A, M1V/A5T/H19L/T36A, M1T/N31D/T32A/T36A/Q38R/S44D/V49A/K50E, M1V/T36A/Q38R/A43V, M1V/L2S/S9P/Q10H/T36A/Q38R/K50G, T36A/Q38R/N53S, M1T/L2S/L35P/T36A/Q38R/T46A/K50R, A5T/A20V/T36A/Q38R, M1T/S16G/I22V/T36A/S44G/T46A/V49A, S16G/T36A, M1I/N11D/S16G/I22M/S29A/T36A/S44G/K50R, M1C/L2C/Q3R/M4E/N11D/S16G/T36P, M1I/N11D/S16G/I22M/S29A/T36A/S44G/K50R, N11D/N31D/T32I/T36A/S44N/N47D/N53D, M1R/L2C/Q3R, H19Y/T36A/S44G, H19Y/T32I/T36A/V49A, H19Y/N31S/T36A/V45A, H19Y/N31S/T36A, H19Y/T36P/T52A, H19Y/N31D/T52M, M1V/H19Y/V45M, S16G/H19Y/N47D, S16G/H19Y/K50T, S16G/H19Y/S44N/K50R, N11D/H19Y/S48T, S9P/N11D/S16R/T32A/Q38R/S44G/T46I/T52A/N53D/A54T, N11D/S16G/S44R, H19L/T32A/S44G/G51E/T52A, S16N/H19Y/T36A/K50R, M1V/H19Y/T36A/R39H/T46A, M1V/H19Y/T36A, H19Y/T36A/N42D/N47S/S48P, M1V/H19Y/T36A/S44G/N47D, M1V/H19Y/T36A/N42R/N53S, H19Y/L35P/T36A/N42D/T46I/V49A, Q3P/S9P/H19Y/N31S/T36A/R39H/N47R/K50E, M1V/H19Y/T36A/N42R/N53S, M1T/H19Y/T36A, M1V/S16N/H19Y/I22M/T36A, M1T/N11D/H19Y/T36A/N42S/V45A/N53S, N11D/S16G/H19Y/T36A/N47S/N53D,

M1V/S9P/Q10P/S16G/H19Y/L26F/T36A/A43V/N53D, S16G/H19Y/T36A/V49A/N53D, S16G/T36A/A43T/S44G/V45M, M4V/S9P/S16G/T36A/Q38R, S9P/N11S/S16G/T36A/Q38R, N11D/E12K/S16R/T36A/T52M, M4V/T32I/T36A/Q38R/A43T/V45A/S48P, S9P/N11D/S16G/Q25R, M1T/A5T/S9P/S16G/Q25R/N31D/V49M, L2S/S9P/S16G/A20T/T32I/Q38R/N42D/T46A/S48L, S16G/Q25R/T46A, G6E/S9A/S16G/Q25R/N31D/N47S/T52M, H19Y/Q38R/T52M, N11D/H19Y/I22M/T32P/N47S/N53S, S16G/H19Y/T36A, S16G/H19Y/T36A/N53D, S9P/N11D/S16G/H19Y/T36A/N47S/N53D, Q3P/S9P/H19Y/N31S/T36A/R39H/N47R/K50E, M1V/L2S/M4T/N11D/H19Y/T36A, M1V/L2S/M4T/N11D/T36A, M1V/L2S/M4T/H19Y/T36I/V45A/V49M, M1V/L2S/M4T/N11D/H19Y/T36A, M1V/L2S/M4T/S9P/Q10R/H19Y/T36A/T46A/N47S, M1V/L2S/M4T/S16G/N31D/T32I/T36A, M1V/M4T/T36A/Q38R/N53K, M1T/N11D/H19Y/T36A/N42S/V45A/N53S, M1T/N31D/T32A/T36A/A38R/S44D/V49A/K50E, M1T/S9P/P23S/Q38R/N42S/S48P/V49A/A54V, H19Y/T36A/S44G, H19Y/T36A, and M4T/T36A/Q38R/N42S/S44G/T46A/N47K/S48P/T52A.

[00248] In some embodiments, the variant sBCMA domain as described herein comprises amino acid substitutions S16G/H19Y/T36A, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

[00249] In some embodiments, the variant sBCMA domain as described herein comprises amino acid substitutions S16G/H19Y/T36A/N53D, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16N, S16R, H19L, A20V, A20T, I22M, I22V,

P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53K, N53S, A54V, and A54T.

[00250] In some embodiments, the variant sBCMA domain as described herein comprises amino acid substitutions S9P/N11D/S16G/H19Y/T36A/N47S/N53D, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, Q10H, Q10P, Q10R, N11S, E12K, F14L, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53K, N53S, A54V, and A54T.

[00251] In some embodiments, the variant sBCMA domain as described herein comprises amino acid substitutions Q3P/S9P/H19Y/N31S/T36A/R39H/N47R/K50E, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16G, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47S, S48L, S48P, S48T, V49A, V49M, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

[00252] In some embodiments, the variant sBCMA domain as described herein comprises amino acid substitutions M1V/L2S/M4T/S16G/N31D/T32I/T36A, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, L2C, Q3P, Q3R, M4E, M4I, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16N, S16R, H19L, H19Y, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31S, T32A, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

[00253] In some embodiments, the variant sBCMA domain as described herein has at least 90% sequence identity to SEQ ID NO: 67.

[00254] In some embodiments, the variant sBCMA domain as described herein has at least 90% sequence identity to SEQ ID NO: 68.

[00255] In some embodiments, the variant sBCMA domain as described herein has at least 90% sequence identity to SEQ ID NO: 69.

[00256] In some embodiments, the variant sBCMA domain as described herein has at least 90% sequence identity to SEQ ID NO: 49.

[00257] In some embodiments, the variant sBCMA domain as described herein has at least 90% sequence identity to SEQ ID NO: 74.

[00258] In some embodiments, the variant sBCMA domain as described herein has SEQ ID NO: 67.

[00259] In some embodiments, the variant sBCMA domain as described herein has SEQ ID NO: 68.

[00260] In some embodiments, the variant sBCMA domain as described herein has SEQ ID NO: 69.

[00261] In some embodiments, the variant sBCMA domain as described herein has SEQ ID NO: 49.

[00262] In some embodiments, the variant sBCMA domain as described herein has SEQ ID NO: 74.

[00263] The Clone Nos., amino acid substitutions as compared to the amino acid sequence of SEQ ID NO:1 and assigned SEQ ID NOs of exemplary variant sBCMA domains are shown in Table 2.

[00264] In some embodiments, the variant sBCMA domain as described herein exhibits enhanced binding affinity for APRIL as compared to SEQ ID NO:1.

[00265] In some embodiments, the variant sBCMA domain as described herein exhibits enhanced binding affinity for BAFF as compared to SEQ ID NO:1.

[00266] In some embodiments, the variant sBCMA domain as described herein exhibits enhanced binding affinity for APRIL and BAFF as compared to SEQ ID NO:1.

4. Fc Domains

[00267] As discussed herein, in addition to sBCMA variant domains described above, the fusion proteins of the invention also include Fc domains of antibodies that generally are based on the IgG class, which has several subclasses, including, but not limited to IgG1, IgG2, and IgG3. As described herein, an Fc domain optionally includes the hinge domain of an IgG antibody.

[00268] Human IgG Fc domains are of particular use in the present invention, and can be derived from the Fc domain from human IgG1, IgG2, or IgG3. In general, IgG1 and IgG2 are used more frequently than IgG3.

[00269] An Fc domain of a human IgG protein included in the fusion protein of the present invention can confer a significant increase in half-life of the fusion protein, and can provide additional binding or interaction with the Ig molecules. In some embodiments, an sBCMA variant – Fc fusion protein can facilitate purification, multimerization, binding and neutralizing other molecules as compared to a monomeric variant sBCMA polypeptide.

[00270] Fc domains can also contain Fc variants to alter function as needed. However, in accordance with many embodiments, Fc variants generally need to retain both the ability to form dimers as well as the ability to bind FcRn. Thus, while many of the embodiments herein rely on the use of a human IgG1 domain, Fc variants can be made to augment or abrogate function in other IgG domains. Thus, for example, ablation variants that reduce or eliminate effector function in IgG1 or IgG2 can be used, and/or FcRn variants that confer tighter binding to the FcRn receptor can be used, as will be appreciated by those in the art.

[00271] In one embodiment, an Fc domain is a human IgG Fc domain or a variant human IgG Fc domain.

[00272] In another embodiment, an Fc domain is human IgG1 Fc domain.

[00273] In a further embodiment, an Fc domain comprises the hinge-CH2-CH3 of human IgG1.

[00274] In another embodiment, an Fc domain comprises the CH2-CH3 of human IgG1.

[00275] In some embodiments, Fc domains can be the Fc domains from other IgGs than IgG1, such as human IgG2 or IgG3. In general, IgG2 is used more frequently than IgG3.

[00276] In an additional embodiment, an Fc domain is a variant human IgG Fc domain. However, the variant Fc domains herein still retain the ability to form a dimer with another Fc domain as measured using known, as well as the ability to bind to FcRn, as this contributes significantly to the increase in serum half life of the fusion proteins herein.

[00277] The variant IgG Fc domain can include an addition, deletion, substitution or any combination thereof compared with the parent human IgG Fc domain.

[00278] In some embodiments, variant human IgG Fc domains of the present invention can have at least about 80%, 85%, 90%, 95%, 95%, 97%, 98% or 99% identity to the corresponding parental human IgG Fc domain (using the identity algorithms discussed above, with one embodiment utilizing the BLAST algorithm as is known in the art, using default parameters).

[00279] In some embodiments, variant human IgG Fc domains of the present invention can have from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 amino acid sequence modifications as compared to the parental human IgG Fc domains.

[00280] In some embodiments, the Fc domain as described herein is a human IgG Fc domain or a variant human IgG Fc domain.

[00281] In some embodiments, the Fc domain as described herein comprises the hinge-CH2-CH3 of human IgG1.

[00282] In some embodiments, the Fc domain as described herein is a variant human IgG Fc domain.

5. Linkers

[00283] The fusion proteins of the invention can include optional linkers to connect the sBCMA domain to the Fc domain.

[00284] By "linker" or "linker peptide" as used herein have a length that is adequate to link two molecules in such a way that they assume the correct conformation relative to one another so that they retain the desired activity. In one embodiment, the linker is from about 1 to 20 amino acids in length, preferably about 1 to 10 amino acids in length. In one embodiment, linkers of 4 to 10 amino acids in length may be used. Useful linkers include IEGRMD or glycine- serine polymers, including for example (GS)n, (GSGGS)n, (GGGGS)n, and (GGGS)n, where n is an integer of at least one (and generally from 3 to 4), glycine-alanine polymers, alanine-serine polymers, and other flexible linkers. Alternatively, a variety of nonproteinaceous polymers, including but not limited to polyethylene glycol (PEG), polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol and polypropylene glycol, may find use as linkers.

[00285] In some embodiments, the linker is a "domain linker", used to link any two domains as outlined herein together, such as to link the variant sBCMA domain with Fc domain. As discussed above, many suitable linkers can be used to allow for recombinant attachment of the two domains with sufficient length and flexibility to allow each domain to retain its biological function. As discussed herein, a particularly useful domain linker is an IEGRMD linker joined to the hinge domain of IgG1.

[00286] In various embodiments, two domains (*e.g.* the sBCMA variant domain and the Fc domain) are generally linked using a domain linker as described herein. In many embodiments, two domains are attached using a flexible linker in such a way that the two domains can act independently. Flexible linkage can be accomplished in a variety of ways, using traditional linkers and/or the hinge linker.

[00287] In some embodiments, the linker as described herein is IEGRMD (SEQ. ID NO. 87).

[00288] In some embodiments, the linker as described herein is GGGGS (SEQ. ID NO. 88).

[00289] In some embodiments, a hinge domain of a human IgG antibody is used. In some cases, a hinge domain can contain amino acid substitutions as well.

[00290] In some embodiments, a domain linker is a combination of a hinge domain and a flexible linker, such as an IgG1 hinge with an IEGRMD linker.

[00291] In one embodiment, a linker is from about 1 to 50 amino acids in length, preferably about 1 to 30 amino acids in length and more preferably about 4 to 10 amino acids.

6. Particular Embodiments of the Invention

[00292] In some embodiments, an sBCMA variant – Fc fusion protein exhibits at least 90%, 95%, 96%, 97%, 98% or 99% identity to SEQ ID NO:80.

[00293] In some embodiments, an sBCMA variant – Fc fusion protein exhibits at least 90%, 95%, 96%, 97%, 98% or 99% identity to SEQ ID NO:81.

[00294] In some embodiments, an sBCMA variant Fc fusion protein exhibits at least 90%, 95%, 96%, 97%, 98% or 99% identity to SEQ ID NO:82.

[00295] In some embodiments, an sBCMA variant – Fc fusion protein exhibits at least 90%, 95%, 96%, 97%, 98% or 99% identity to SEQ ID NO:83.

[00296] In some embodiments, an sBCMA variant – Fc fusion protein exhibits at least 90%, 95%, 96%, 97%, 98% or 99% identity to SEQ ID NO:84.

[00297] In some embodiments, an sBCMA variant – Fc fusion protein has the amino acid sequence as set forth in SEQ ID NO:80.

[00298] In some embodiments, an sBCMA variant – Fc fusion protein has the amino acid sequence as set forth in SEQ ID NO:81.

[00299] In some embodiments, an sBCMA variant – Fc fusion protein has the amino acid sequence as set forth in SEQ ID NO:82.

[00300] In some embodiments, an sBCMA variant – Fc fusion protein has the amino acid sequence as set forth in SEQ ID NO:83.

[00301] In some embodiments, an sBCMA variant – Fc fusion protein has the amino acid sequence as set forth in SEQ ID NO:84.

E. Methods of Treatment

1. Subjects amenable to treatment

[00302] Various embodiments are directed to methods comprising administering to a subject in need of treatment a therapeutically effective amount of one or more variant sBCMA proteins as described herein.

[00303] Various embodiments are directed to methods comprising administering to a subject in need of treatment a therapeutically effective amount of one or more sBCMA variant – Fc fusion proteins as described herein.

[00304] In some embodiments, the present invention provides methods of reducing immunoglobulin production in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant protein(s).

[00305] In some embodiments, the present invention provides methods of reducing production of IgA, IgM and/or IgG in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant protein(s).

[00306] In some embodiments, the present invention provides methods of reducing production of IgA, IgM or both in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant protein(s). In some embodiments, the present invention provides methods of reducing production of IgA, IgG or both in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant protein(s). In some embodiments, the present invention provides methods of reducing production of IgG, IgM or both in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant protein(s).

[00307] In some embodiments, the present invention provides methods of reducing production of IgA in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant protein(s). In some embodiments, the present invention provides methods of reducing production of IgM in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant protein(s). In some embodiments, the present invention provides methods of reducing production of IgG in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant protein(s).

[00308] In some embodiments, the present invention provides methods of reducing production of IgA and IgM in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant protein(s). In some embodiments, the present invention provides methods of reducing production of IgA and IgG in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant protein(s). In some embodiments, the present invention provides methods of reducing production of IgG and IgM in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant protein(s).

[00309] In some embodiments, the present invention provides methods of reducing production of IgA, IgM and IgG in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant protein(s).

[00310] In some embodiments, the method as disclosed herein does not affect normal B cell viability. In some embodiments, the subject is diagnosed with an autoimmune disease. In some embodiments, the subject is diagnosed with fibrosis. In some embodiments, the subject is human.

[00311] In some embodiments, the present invention provides methods of reducing immunoglobulin production in subjects diagnosed with autoimmune disease(s) and/or

fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s).

[00312] In some embodiments, the present invention provides methods of reducing production of IgA, IgM and/or IgG in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s).

[00313] In some embodiments, the present invention provides methods of reducing production of IgA, IgM or both in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s). In some embodiments, the present invention provides methods of reducing production of IgA, IgG or both in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s). In some embodiments, the present invention provides methods of reducing production of IgG, IgM or both in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s).

[00314] In some embodiments, the present invention provides methods of reducing production of IgA in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s). In some embodiments, the present invention provides methods of reducing production of IgM in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s). In some embodiments, the present invention provides methods of reducing production of IgG in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s).

[00315] In some embodiments, the present invention provides methods of reducing production of IgA and IgM in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s). In some embodiments, the present invention provides methods of reducing production of IgA and IgG in subjects diagnosed with autoimmune disease(s)

and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s). In some embodiments, the present invention provides methods of reducing production of IgG and IgM in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s).

[00316] In some embodiments, the present invention provides methods of reducing production of IgA, IgM and IgG in subjects diagnosed with autoimmune disease(s) and/or fibrosis comprising administering to the subjects a therapeutically effective dose of sBCMA variant – Fc fusion protein(s).

[00317] In some embodiments, the method as disclosed herein does not affect normal B cell viability. In some embodiments, the subject is diagnosed with an autoimmune disease. In some embodiments, the subject is diagnosed with fibrosis. In some embodiments, the subject is human.

[00318] The present invention provides *inter alia,* a method of reducing production of IgA, IgM, and/or IgG in a subject diagnosed with an autoimmune disease and/or fibrosis, said method comprising administering to the subject a therapeutically effective dose of an sBCMA variant protein and/or sBCMA variant -Fc fusion protein. In some embodiments, the present invention provides *inter alia,* a method of reducing production of IgA, IgM, and/or IgG in a subject diagnosed with an autoimmune disease, said method comprising administering to the subject a therapeutically effective dose of an sBCMA variant protein. In some embodiments, the present invention provides *inter alia,* a method of reducing production of IgA, IgM, and/or IgG in a subject diagnosed with an autoimmune disease, said method comprising administering to the subject a therapeutically effective dose of an sBCMA variant -Fc fusion protein. In some embodiments, the present invention provides *inter alia,* a method of reducing production of IgA, IgM, and/or IgG in a subject diagnosed with fibrosis, said method comprising administering to the subject a therapeutically effective dose of an sBCMA variant protein. In some embodiments, the present invention provides *inter alia,* a method of reducing production of IgA, IgM, and/or IgG in a subject diagnosed with fibrosis, said method comprising administering to the subject a therapeutically effective dose of an sBCMA variant -Fc fusion protein.

[00319] In some embodiments, the invention provides a method of reducing production of IgA, IgM, and/or IgG in a subject diagnosed with an autoimmune disease or fibrosis, said method comprising administering to the subject a therapeutically effective dose of an sBCMA variant-Fc fusion protein, wherein the sBCMA variant-Fc fusion protein comprises:

a) a variant sBCMA domain comprising at least one amino acid substitution as compared to SEQ ID NO:1, wherein said amino acid substitution is at a position number selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 14, 16, 19, 20, 22, 23, 25, 26, 29, 31, 32, 35, 36, 38, 39, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, and 54, wherein the numbering is according to the EU index;

b) an optional linker; and

c) an Fc domain.

[00320] In some embodiments, the invention provides the method as disclosed herein, wherein normal B cell viability is not altered.

[00321] In some embodiments, the invention provides the method as disclosed herein, wherein the subject is diagnosed with the autoimmune disease.

[00322] In some embodiments, the invention provides the method as disclosed herein, wherein the method reduces production of IgA.

[00323] In some embodiments, the invention provides the method as disclosed herein, wherein the method reduces production of IgG.

[00324] In some embodiments, the invention provides the method as disclosed herein, wherein the method reduces production of IgM.

[00325] In some embodiments, the invention provides the method as disclosed herein, wherein the method reduces production of both IgA and IgM.

[00326] In some embodiments, the invention provides the method as disclosed herein, wherein the method reduces production of both IgA and IgG.

[00327] In some embodiments, the invention provides the method as disclosed herein, wherein the method reduces production of IgM and IgG.

[00328] In some embodiments, the invention provides the method as disclosed herein, wherein the method reduces production of both IgA, IgM and IgG.

[00329] In some embodiments, the invention provides the method as disclosed herein, wherein the autoimmune disease is selected from the group consisting of IgA Nephropathy, Systemic Lupus Erythematosus, Churg-Strauss Syndrome, Myasthenia Gravis, Multiple Sclerosis, and rheumatoid arthritis.

[00330] In some embodiments, the invention provides the method as disclosed herein, wherein the subject is diagnosed with the fibrosis.

[00331] In some embodiments, the invention provides the method as disclosed herein, wherein the fibrosis is selected from the group consisting of idiopathic pulmonary fibrosis, non-alcoholic steatohepatitis, scleroderma, and kidney fibrosis.

[00332] In some embodiments, the invention provides the method as disclosed herein, wherein said fusion protein comprises, from N- to C-terminal:

a) said variant sBCMA domain;

b) said optional linker; and

c) said Fc domain.

[00333] In some embodiments, the invention provides the method as disclosed herein, wherein said fusion protein comprises, from N- to C-terminal:

a) said Fc domain;

b) said optional linker; and

c) said variant sBCMA domain.

[00334] In some embodiments, the invention provides the method as disclosed herein, wherein said variant sBCMA domain has at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO:1.

[00335] In some embodiments, the invention provides the method as disclosed herein, wherein said amino acid substitution(s) occur at one of said positions, two of said positions, three of said positions, four of said positions, five of said positions, six of said positions, seven of said positions, eight of said positions, or nine of said positions.

[00336] In some embodiments, the invention provides the method as disclosed herein, wherein said amino acid substitution(s) is selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16G, S16N, S16R, H19L, H19Y, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36A, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

[00337] In some embodiments, the invention provides the method as disclosed herein, wherein said amino acid substitution(s) is selected from the group consisting of M1V, L2S, Q3P, M4T, S9P, N11D, S16G, H19Y, N31S, N31D, T32I, T36A, R39H, N47S, K50E, and N53E.

[00338] In some embodiments, the invention provides the method as disclosed herein, wherein said amino acid substitution(s) is selected from the group consisting of S16G, H19Y and T36A.

[00339] In some embodiments, the invention provides the method as disclosed herein, wherein said amino acid substitutions are selected from the group consisting of L2S/S9P/E12K/N31D/T36A/N42S/N53S, M1V/T32P/T36A/T46I/N53D/A54V, Q3R/S16N/T36A/A43T, F14L/S16G/T36A/V45A/N47D, M1T/M4V/S9F/S16G/T32A/Q38R, M1A/S9A/Q38R, G6E/Q25R/Q38R, M1V/M4I/G6E/S9P/N11D/V49M/T52M/A54V, N11D/S16G/N31S, N11D/H19Y/I22M/T32P/N47S/N53S, G6E/Q7R/H19Y/L35S, H19Y/N42D/S48P/T52A, M1V/N31D/T32I/T36A, M1V/A5T/H19L/T36A, M1T/N31D/T32A/T36A/Q38R/S44D/V49A/K50E, M1V/T36A/Q38R/A43V, M1V/L2S/S9P/Q10H/T36A/Q38R/K50G, T36A/Q38R/N53S, M1T/L2S/L35P/T36A/Q38R/T46A/K50R, A5T/A20V/T36A/Q38R, M1T/S16G/I22V/T36A/S44G/T46A/V49A, S16G/T36A, M1I/N11D/S16G/I22M/S29A/T36A/S44G/K50R, M1C/L2C/Q3R/M4E/N11D/S16G/T36P, M1I/N11D/S16G/I22M/S29A/T36A/S44G/K50R, N11D/N31D/T32I/T36A/S44N/N47D/N53D, M1R/L2C/Q3R, H19Y/T36A/S44G,

H19Y/T32I/T36A/V49A, H19Y/N31S/T36A/V45A, H19Y/N31S/T36A, H19Y/T36P/T52A, H19Y/N31D/T52M, M1V/H19Y/V45M, S16G/H19Y/N47D, S16G/H19Y/K50T, S16G/H19Y/S44N/K50R, N11D/H19Y/S48T, S9P/N11D/S16R/T32A/Q38R/S44G/T46I/T52A/N53D/A54T, N11D/S16G/S44R, H19L/T32A/S44G/G51E/T52A, S16N/H19Y/T36A/K50R, M1V/H19Y/T36A/R39H/T46A, M1V/H19Y/T36A, H19Y/T36A/N42D/N47S/S48P, M1V/H19Y/T36A/S44G/N47D, M1V/H19Y/T36A/N42R/N53S, H19Y/L35P/T36A/N42D/T46I/V49A, Q3P/S9P/H19Y/N31S/T36A/R39H/N47R/K50E, M1V/H19Y/T36A/N42R/N53S, M1T/H19Y/T36A, M1V/S16N/H19Y/I22M/T36A, M1T/N11D/H19Y/T36A/N42S/V45A/N53S, N11D/S16G/H19Y/T36A/N47S/N53D, M1V/S9P/Q10P/S16G/H19Y/L26F/T36A/A43V/N53D, S16G/H19Y/T36A/V49A/N53D, S16G/T36A/A43T/S44G/V45M, M4V/S9P/S16G/T36A/Q38R, S9P/N11S/S16G/T36A/Q38R, N11D/E12K/S16R/T36A/T52M, M4V/T32I/T36A/Q38R/A43T/V45A/S48P, S9P/N11D/S16G/Q25R, M1T/A5T/S9P/S16G/Q25R/N31D/V49M, L2S/S9P/S16G/A20T/T32I/Q38R/N42D/T46A/S48L, S16G/Q25R/T46A, G6E/S9A/S16G/Q25R/N31D/N47S/T52M, H19Y/Q38R/T52M, N11D/H19Y/I22M/T32P/N47S/N53S, S16G/H19Y/T36A, S16G/H19Y/T36A/N53D, S9P/N11D/S16G/H19Y/T36A/N47S/N53D, Q3P/S9P/H19Y/N31S/T36A/R39H/N47R/K50E, M1V/L2S/M4T/N11D/H19Y/T36A, M1V/L2S/M4T/N11D/T36A, M1V/L2S/M4T/H19Y/T36I/V45A/V49M, M1V/L2S/M4T/N11D/H19Y/T36A, M1V/L2S/M4T/S9P/Q10R/H19Y/T36A/T46A/N47S, M1V/L2S/M4T/S16G/N31D/T32I/T36A, M1V/M4T/T36A/Q38R/N53K, M1T/N11D/H19Y/T36A/N42S/V45A/N53S, M1T/N31D/T32A/T36A/A38R/S44D/V49A/K50E, M1T/S9P/P23S/Q38R/N42S/S48P/V49A/A54V, H19Y/T36A/S44G, H19Y/T36A, and M4T/T36A/Q38R/N42S/S44G/T46A/N47K/S48P/T52A.

[00340] In some embodiments, the invention provides the method as disclosed herein, wherein said variant sBCMA domain comprises the amino acid substitutions S16G/H19Y/T36A, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L,

S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

[00341] In some embodiments, the invention provides the method as disclosed herein, wherein said variant sBCMA domain comprises the amino acid substitutions S16G/H19Y/T36A/N53D, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53K, N53S, A54V, and A54T.

[00342] In some embodiments, the invention provides the method as disclosed herein, wherein said variant sBCMA domain comprises the amino acid substitutions S9P/N11D/S16G/H19Y/T36A/N47S/N53D, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, Q10H, Q10P, Q10R, N11S, E12K, F14L, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53K, N53S, A54V, and A54T.

[00343] In some embodiments, the invention provides the method as disclosed herein, wherein said variant sBCMA domain comprises the amino acid substitutions Q3P/S9P/H19Y/N31S/T36A/R39H/N47R/K50E, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16G, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R,

L26F, S29A, N31D, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47S, S48L, S48P, S48T, V49A, V49M, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

[00344] In some embodiments, the invention provides the method as disclosed herein, wherein said variant sBCMA domain comprises the amino acid substitutions M1V/L2S/M4T/S16G/N31D/T32I/T36A, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, L2C, Q3P, Q3R, M4E, M4I, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16N, S16R, H19L, H19Y, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31S, T32A, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

[00345] In some embodiments, the invention provides the method as disclosed herein, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 67.

[00346] In some embodiments, the invention provides the method as disclosed herein, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 68.

[00347] In some embodiments, the invention provides the method as disclosed herein, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 69.

[00348] In some embodiments, the invention provides the method as disclosed herein, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 49.

[00349] In some embodiments, the invention provides the method as disclosed herein, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 74.

[00350] In some embodiments, the invention provides the method as disclosed herein, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 67.

[00351] In some embodiments, the invention provides the method as disclosed herein, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 68.

[00352] In some embodiments, the invention provides the method as disclosed herein, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 69.

[00353] In some embodiments, the invention provides the method as disclosed herein, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 49.

[00354] In some embodiments, the invention provides the method as disclosed herein, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 74.

[00355] In some embodiments, the invention provides the method as disclosed herein, wherein said Fc domain is a human IgG Fc domain or a variant human IgG Fc domain.

[00356] In some embodiments, the invention provides the method as disclosed herein, wherein said human IgG Fc domain comprises the hinge-CH2-CH3 of human IgG1.

[00357] In some embodiments, the invention provides the method as disclosed herein, wherein said Fc domain is a variant human IgG Fc domain.

[00358] In some embodiments, the invention provides the method as disclosed herein, wherein said Fc domain is a human IgG1 Fc domain.

[00359] In some embodiments, the invention provides the method as disclosed herein, wherein said linker is SEQ ID NO:87.

[00360] In some embodiments, the invention provides the method as disclosed herein, wherein said linker is selected from the group consisting of (GS)n, (GSGGS)n, (GGGGS)n, and (GGGS)n, wherein n is selected from the group consisting of 1, 2, 3, 4 and 5.

[00361] In some embodiments, the invention provides the method as disclosed herein, wherein said linker is SEQ ID NO:88.

[00362] In some embodiments, the invention provides the method as disclosed herein, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:80.

[00363] In some embodiments, the invention provides the method as disclosed herein, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:81.

[00364] In some embodiments, the invention provides the method as disclosed herein, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:82.

[00365] In some embodiments, the invention provides the method as disclosed herein, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:83.

[00366] In some embodiments, the invention provides the method as disclosed herein, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:84.

2. Therapeutic administration

[00367] In certain embodiments, a therapeutically effective composition or formulation having one or more variant sBCMA proteins may be administered systemically to the individual or via any other route of administration known in the art.

[00368] In certain embodiments, a therapeutically effective composition or formulation having one or more sBCMA variant – Fc fusion proteins may be administered systemically to the individual or via any other route of administration known in the art.

3. Dosing

[00369] In some embodiments, an effective dose of the therapeutic entity of the present invention, *e.g.* for the treatment of fibrotic and/or immunomodulatory disorders, varies depending upon many different factors, including means of administration, target site, physiological state of the patient, whether the patient is human or an animal, other medications administered, and whether treatment is prophylactic or therapeutic. Treatment dosages can be titrated to optimize safety and efficacy.

VI. EXAMPLES

A. EXAMPLE 1: Cynomolgus Monkey Single Dose Toxicity Study

[00370] The purposes of this study were to evaluate the acute toxicity after single administration of AB001 (sBCMA clone #71-Fc fusion protein) via intravenous infusion in cynomolgus monkeys, to provide the maximum tolerated dose (MTD) as reference for the design of subsequent toxicity studies and clinical trials, and to characterize the toxicokinetics and immunogenicity. A total of ten Cynomolgus monkeys (1 animal/gender/group) were assigned into 5 groups and given a single intravenous infusion of sBCMA variant - Fc fusion protein (0.1, 1, 10 and 100 mg/kg) or vehicle and observed for 6 weeks. The dose volume was adjusted as per the latest body weight of animals. The actual infusion duration did not exceed 5% of the nominal infusion duration (**Figure 1**).

[00371] Parameters evaluated included clinical observations, body weights, food consumption, hematology, coagulation, plasma chemistry, lymphocyte immunophenotype, immunoglobulin,cytokines and gross pathology. Clinical observations were conducted daily from the day next to the randomization to experimental completion according to the frequencies listed. Non-dosing day: once in the morning and once in the afternoon. Dosing days: once at pre-dose, once within 1h and 3h to 6h post-dose. Body weight monitored during Pre-dose phase: once on Day -13 and Day -6, respectively, followed by once on days 1, 2, 7, 14, 21, 28, 35 and 42 post-dose. Blood collection were performed during pre-dose phase: Day -13, Day -6, Day -3 (M1305, M1407), Day 1 (pre-dose) and dosing phase: 4 times, Days 2, 7, 14 and 42, among which coagulation wasnot included on Days 7 and 14. The animals were necropsied at the end of observation period (Day 43), Animals were fasted overnight (no longer than 24 hours) before necropsy (**Figure 1**). In conclusion, no drug-related abnormalities of body weight were observed in the animals of each groupduring the observation period (**Figure 4**). Hematology findings include: 100 mg/kg: A decrease (by 56%) of LYMP was noted in the male animal (**Figure 5A**) on Day 2 and in the female animal on Day 7 (by 57%) (**Figure 5B**) when comparing with the pre-dose value on Day 1. 10 mg/kg: A decrease (by 31%) of LYMP was noted in the female animal on Day 7 when comparing with the pre-dose value on Day 1 (**Figure 5B**). No significant abnormalities were noted in the male animal (**Figure 5A**). 1 mg/kg: A decrease (by 26%) of LYMP was noted in the female animal on Day 7 when comparing with the pre-dose value on Day 1 (Figure 5B). No significant abnormalities were noted in the male animal. 0.1 mg/kg: No significant abnormalities were noted in the female or male animals (**Figure 5**). Declines of RBC, HGB, and HCT were observed in the female and male animals of each group on Day 2, Day 7,

and/or Day 14. Considering that much blood were sampled during the experiment, it was considered that the decreases in RBC, HGB, and HCT might be related to the blood sampling **(Figures 8 to 11)**. No abnormalities of coagulation parameters were noted in the female or male animals of each group **(Figures 12 to 13)**. No abnormalities of plasma chemistry parameters were noted in the female or male animals of each group **(Figures 14 to 19)**. No abnormalities of immunophenotype were noted in the female or male animals of each group. No pathological gross abnormalities were present in any animal **(Figures 2 and 3)**. Cytokine analysis showed at 100 mg/kg, an increase of IL-10, IFN-γ, IL-17A were noted in the male animal on Day 1, Day 2or Day 3 when comparing with the pre-dose value or the vehicle **(Figures 20 and 21)**. No abnormalities of cytokines were noted in the female animal **(Figures 22 and 23)**. No abnormalities of cytokines were noted in the female or male animals of other groups. Importantly, differences were noted in immunoglobulin levels in both female and male treated groups. Specifically, 100 mg/kg: Decreases of IgA, IgM, and/or IgG were noted in the female and/or male animals during Day 2 to Day 42 when comparing with the pre-dose value. 10 mg/kg: Decreases of IgA, IgM, and/or IgG were noted in the female and/or male animal during Day 7 to Day 42 when comparing with the pre-dose value. 1 mg/kg: Decreases of IgA and IgM were noted in the female and/or male animals on Day 7and Day 14 when comparing with the pre-dose value. 0.1 mg/kg: No abnormalities of immunoglobulin were noted in the female or male animals **(Figures 6 and 7, Figures 16 and 19)**.

B. EXAMPLE 2: Cell Development and Clone Selection

[00372] CHO-K1-C6-4G5 host cells thawed from CHO-K1-C6-4G5 SCB cell bank, has been maintained in exponential phase with HyCell TranFx-C medium in several passages. On the day of transfection, cells were adjusted to viable cell density 1E+06 cells/mL in 27 mL cell culture (125 mL shake flask). Transfection mixtures was prepared by diluting 50 µg of linearized expression plasmid in 2.5 mL OptiPRO SFM. The FreeStyle MAX solution was then mixed with the DNA solution and left at room temperature for 10~20 minutes. After incubation, the solution was added into the CHO-K1-C6 culture (25 mL in a 125 mL shake flask). Transfected cells were incubated in a 130 rpm, 37°C, 5% CO_2

incubator. One portion of transfected cells were used for stable pools generation post transfection 48 hours.

[00373] 48 hours post transfection, transfected cells were subjected to drug selection. Cells were seeded at density of 5 E+05 cells/mL in 30 mL medium (HyCell TransFx-C containing 4 mM L-glutamine and 0.1% F-68) in a 150T Flask with selection drugs (15 µg/mL Puromycin + 800 nM MTX). Cells were incubated in a 37°C, 8% CO_2 static incubator for Day 0.

[00374] After 5 to 7 days, cell viability would drop to 15 to 25%. Cell cultures were centrifugation at 200 g, 5 minutes, 22 °C. Cell culture media were removed and cell pellets were re-suspended in 10 mL fresh selective medium in a 75T Flask, incubated in a 37°C, 8% CO_2 static incubator. In another 10 to 15 days, cells would then gradually recovered to 40 to 60% viability and kept in a 10 mL culture in a 75T Flask. Once cell viability achieved more than 50~60%, cells would be expanded to 20~25 mL culture in a 125 mL shake flask, incubated in a 130 rpm, 37°C, 5% CO_2 incubator. In another 8 to 10 days, each pool would recovery to about 90% viability. Once each pool reached 90% viability by the subsequent culture, cryopreservation was performed for at least 2 vials per pool.

[00375] Upon all pools recovered to 90% viability and cryopreservation was done, each pool would be thawed and evaluated by 11 days Fed-batch culture experiment. Inoculating each pool of cells at viable cell density of ~5.5E+05 cells/mL in two different 10 mL medium HyCell CHO or BalanCD CHO in a 50mL Spin tube, incubated in a 180 rpm, 37°C, 5%CO_2 incubator as Day0. Viable cell density and viability were recorded by BIORAD TC20 cell counter **(Figure 24A and B).**

[00376] Cell culture fluids were harvested on day 11 and followed by centrifugation at 2000 g, 20 minutes, 22 °C. The culture supernatants were passed through a 0.22 µm filter and ready for titer determination. A portion of filtered supernatants was the source materials for the purification of sBCMA variant – Fc fusion protein clones using GE Protein A HP SpinTrap column. ProA purified materials were subjected to non-reduced and reduced SDS-PAGE **(Figure 25A and B)**.

[00377] Two pools of sBCMA variant – Fc fusion proteins were choosen based on their titer and performance were thawed and adapted to HyCell CHO medium containing 4

mM L-glutamine with 15 μg/mL Puromycin and 800 nM MTX or 60 μg/mL Puromycin and 3000 nM MTX about a week. Pools were kept at the exponential phase, incubated in a 130 rpm, 37°C and 5% CO_2 incubator. One day before the day of SCC experiment, cells were seeded at viable cell density 5~7E+05 cells/mL with selective drugs. On the day of SCC experiment, the condition of the cells should achieve viable cell density ~ 1.4E+06 cells/mL, viability >= 90%. 200 μL cloning medium was dispensed into each well of the 96 well plate. There were 4 plates for each pool. Each plate was labeled with a barcode. Using a cell strainer such as 40 μm nylon mesh cell strainer to obtain a uniform single cell suspension at least 3 mL. Cells were then adjusted to viable cell density ~7E+05 cells/mL in HyCell CHO medium with 4 mM L-glutamine. Load 70 μL of the cells into the cartridge of SCP™. The parameter of single cell printer was set to dispense single cell into each well in a 96 well plate. The plates were then centrifugation at 200 g, 22°C for 5 minutes. Images were taken by CloneSelect Imager (CSI) under high resolution mode for day 0, 1 and 2. The plates were then incubated in a 37°C, 8% CO_2 static incubator. On day 14 or 18, images were taken by CSI again.

[00378] There were 35 and 22 clones picked from 96 well plates of two sBCMA variant – Fc fusion protein pools respectively. Some clones were not be able to grow as the concentration of selection drugs was gradually increased back to 100% selection pressure during a scale-up process. Ultimately, clones that were able to grow in a 50 mL Spin tube and eventually achieved >= 95% viability and the viable cell density >= 1E+06 cells/mL would be cryopreserved. There were 40 clones cryopreserved.

[00379] 40 clones from two pools were screened by the experiment of 12 day Fed batch culture. Cells from each clone were cultured at viable cell density 5.5E+05 cells/mL in a total 10 mL No selective drug medium (HyCell CHO containing 6 mM L-gln) in a 50 mL Spin tube, incubated in a 180 rpm, 37°C, 5% CO_2 incubator. Cell culture fluids were harvested on day 12 and followed by centrifugation at 2000 g, 20 minutes, 22 °C. The culture supernatants were passed through a 0.22 μm filter and ready for titer determination using ProA-HPLC. A portion of filtered supernatants was the source materials for the purification of JHL9931 antibodies using GE Protein A HP SpinTrap column. Top clones were chosen based on ProA-HPLC titer and Day12 cell viability **(Figure 26)**. In addition,

Purified ProA materials from top clones were subjected to UPLC-FLR analysis for N-glycan profiles **(Figure 27)**.

[00380] The examples set forth above are provided to give those of ordinary skill in the art a complete disclosure and description of how to make and use the embodiments of the compositions, systems and methods of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Modifications of the above-described modes for carrying out the invention that are obvious to persons of skill in the art are intended to be within the scope of the following claims. All patents and publications mentioned in the specification are indicative of the levels of skill of those skilled in the art to which the invention pertains. All references cited in this disclosure are incorporated by reference to the same extent as if each reference had been incorporated by reference in its entirety individually.

[00381] All headings and section designations are used for clarity and reference purposes only and are not to be considered limiting in any way. For example, those of skill in the art will appreciate the usefulness of combining various aspects from different headings and sections as appropriate according to the spirit and scope of the invention described herein.

[00382] All references cited herein are hereby incorporated by reference herein in their entireties and for all purposes to the same extent as if each individual publication or patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

[00383] Many modifications and variations of this application can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments and examples described herein are offered by way of example only.

C. EXAMPLE 3: Evaluation of sBCMA Variants on lupus model in NZBWF1/J mice + Pristane

[00384] The effect of test articles on the Lupus model in NZBWF1/J mice with an intraperitoneal injection of pristane was evaluated. NZBWF1/J mice of 11 - 12 weeks were randomly assigned into 4 groups, and animals in the model groups received pristane. C57BL/6 mouse was used as normal control.

[00385] The NZB/W F1 mice is a classical lupus model generated by the F1 hybrid between the NZB and NZW strains. These hybrid mice develop severe lupus-like phenotypes, similar to that in lupus patients. These lupus-like phenotypes include lymphadenopathy, splenomegaly, elevated serum antinuclear autoantibodies (ANA) including anti-dsDNA IgG, and immune complex-mediated glomerulonephritis (GN). As for SLE patients, disease in the NZB/W F1 strain is strongly biased towards females, which is in part due to estrogen levels.

[00386] Intraperitoneal injection of pristane stimulates the formation of lupus-associated autoantibodies against multiple nuclear antigens. This leads to chronic inflammation with the development of lupus-like autoimmunity, which particularly includes the formation of antibodies characteristic of SLE as well as immune-complex nephritis with a high degree of similarity to human SLE.

[00387] 48 NZBWF1/J mice was randomized into 4 groups, 12 in each group based on body weight and urine protein level before the experiment. All NZBWF1/J mice received pristane in a volume of 0.5mL by intraperitoneal injection. Group 1 received saline vehicle control with pristane. Group 2 received 10mg/kg Telitacicept twice a week with pristane. Group 3 received 1 mg/kg sBCMA variant twice a week with pristane. Group 4 received 10mg/kg sBCMA variant twice a week with pristane.

[00388] Level of proteinuria (mg/ml) was measured on day 14 post treatment, a reduction in proteinuria level was observed in treatment groups 2, 3 and 4 **(Figure 31)**. Lymph node swelling score was recorded **(Figure 32)**. Vehicle treated group was presented with highest score of lymph node swelling compared to other treatment groups and animals treated with 10mg/kg of sBCMA variant observed no lymph node swelling.

WHAT IS CLAIMED IS:

1. A method of reducing production of IgA, IgM, and/or IgG in a subject diagnosed with an autoimmune disease or fibrosis, said method comprising administering to the subject a therapeutically effective dose of a soluble B-cell maturation antigen (sBCMA) variant-Fc fusion protein, wherein the sBCMA variant-Fc fusion protein comprises:

a) a variant sBCMA domain comprising at least one amino acid substitution as compared to SEQ ID NO:1, wherein said amino acid substitution is at a position number selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 14, 16, 19, 20, 22, 23, 25, 26, 29, 31, 32, 35, 36, 38, 39, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, and 54, wherein the numbering is according to the EU index;

b) an optional linker; and

c) an Fc domain.

2. The method according to claim 1, wherein normal B cell viability is not altered.

3. The method according to claim 1 or claim 2, wherein the method reduces production of IgA.

4. The method according to claim 1 or claim 2, wherein the method reduces production of IgM.

5. The method according to claim 1 or claim 2, wherein the method reduces production of IgG.

6. The method according to claim 1 or claim 2, wherein the method reduces production of both IgA and IgM.

7. The method according to claim 1 or claim 2, wherein the method reduces production of both IgA and IgG.

8. The method according to claim 1 or claim 2, wherein the method reduces production of both IgM and IgG.

9. The method according to claim 1 or claim 2, wherein the method reduces production of IgA, IgM and IgG.

10. The method according to any one of the preceding claims, wherein the subject is diagnosed with the autoimmune disease.

11. The method according to claim 10, wherein the autoimmune disease is selected from the group consisting of IgA Nephropathy, Systemic Lupus Erythematosus, Churg-Strauss Syndrome, Myasthenia Gravis, Multiple Sclerosis, and rheumatoid arthritis.

12. The method according to any one of the preceding claims, wherein the subject is diagnosed with the fibrosis.

13. The method according to claim 12, wherein the fibrosis is selected from the group consisting of idiopathic pulmonary fibrosis, non-alcoholic steatohepatitis, scleroderma, and kidney fibrosis.

14. The method according to any one of the preceding claims, wherein said fusion protein comprises, from N- to C-terminal:

a) said variant sBCMA domain;

b) said optional linker; and

c) said Fc domain.

15. The method according to any one of claims 1-13, wherein said fusion protein comprises, from N- to C-terminal:

a) said Fc domain;

b) said optional linker; and

c) said variant sBCMA domain.

16. The method according to any one of the preceding claims, wherein said variant sBCMA domain has at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO:1.

17. The method according to any one of the preceding claims, wherein said amino acid substitution(s) occur at one of said positions, two of said positions, three of said positions, four of said positions, five of said positions, six of said positions, seven of said positions, eight of said positions, or nine of said positions.

18. The method according to any one of the preceding claims, wherein said amino acid substitution(s) is selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16G, S16N, S16R, H19L, H19Y, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36A, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

19. The method according to any one of the preceding claims, wherein said amino acid substitution(s) is selected from the group consisting of M1V, L2S, Q3P, M4T, S9P, N11D, S16G, H19Y, N31S, N31D, T32I, T36A, R39H, N47S, K50E, and N53E.

20. The method according to any one of the preceding claims, wherein said amino acid substitution(s) is selected from the group consisting of S16G, H19Y and T36A.

21. The method according to any one of claims 1-18, wherein said amino acid substitutions are selected from the group consisting of L2S/S9P/E12K/N31D/T36A/N42S/N53S, M1V/T32P/T36A/T46I/N53D/A54V, Q3R/S16N/T36A/A43T, F14L/S16G/T36A/V45A/N47D, M1T/M4V/S9F/S16G/T32A/Q38R, M1A/S9A/Q38R, G6E/Q25R/Q38R, M1V/M4I/G6E/S9P/N11D/V49M/T52M/A54V, N11D/S16G/N31S, N11D/H19Y/I22M/T32P/N47S/N53S, G6E/Q7R/H19Y/L35S, H19Y/N42D/S48P/T52A, M1V/N31D/T32I/T36A, M1V/A5T/H19L/T36A, M1T/N31D/T32A/T36A/Q38R/S44D/V49A/K50E, M1V/T36A/Q38R/A43V, M1V/L2S/S9P/Q10H/T36A/Q38R/K50G, T36A/Q38R/N53S, M1T/L2S/L35P/T36A/Q38R/T46A/K50R, A5T/A20V/T36A/Q38R, M1T/S16G/I22V/T36A/S44G/T46A/V49A, S16G/T36A,

M1I/N11D/S16G/I22M/S29A/T36A/S44G/K50R, M1C/L2C/Q3R/M4E/N11D/S16G/T36P, M1I/N11D/S16G/I22M/S29A/T36A/S44G/K50R, N11D/N31D/T32I/T36A/S44N/N47D/N53D, M1R/L2C/Q3R, H19Y/T36A/S44G, H19Y/T32I/T36A/V49A, H19Y/N31S/T36A/V45A, H19Y/N31S/T36A, H19Y/T36P/T52A, H19Y/N31D/T52M, M1V/H19Y/V45M, S16G/H19Y/N47D, S16G/H19Y/K50T, S16G/H19Y/S44N/K50R, N11D/H19Y/S48T, S9P/N11D/S16R/T32A/Q38R/S44G/T46I/T52A/N53D/A54T, N11D/S16G/S44R, H19L/T32A/S44G/G51E/T52A, S16N/H19Y/T36A/K50R, M1V/H19Y/T36A/R39H/T46A, M1V/H19Y/T36A, H19Y/T36A/N42D/N47S/S48P, M1V/H19Y/T36A/S44G/N47D, M1V/H19Y/T36A/N42R/N53S, H19Y/L35P/T36A/N42D/T46I/V49A, Q3P/S9P/H19Y/N31S/T36A/R39H/N47R/K50E, M1V/H19Y/T36A/N42R/N53S, M1T/H19Y/T36A, M1V/S16N/H19Y/I22M/T36A, M1T/N11D/H19Y/T36A/N42S/V45A/N53S, N11D/S16G/H19Y/T36A/N47S/N53D, M1V/S9P/Q10P/S16G/H19Y/L26F/T36A/A43V/N53D, S16G/H19Y/T36A/V49A/N53D, S16G/T36A/A43T/S44G/V45M, M4V/S9P/S16G/T36A/Q38R, S9P/N11S/S16G/T36A/Q38R, N11D/E12K/S16R/T36A/T52M, M4V/T32I/T36A/Q38R/A43T/V45A/S48P, S9P/N11D/S16G/Q25R, M1T/A5T/S9P/S16G/Q25R/N31D/V49M, L2S/S9P/S16G/A20T/T32I/Q38R/N42D/T46A/S48L, S16G/Q25R/T46A, G6E/S9A/S16G/Q25R/N31D/N47S/T52M, H19Y/Q38R/T52M, N11D/H19Y/I22M/T32P/N47S/N53S, S16G/H19Y/T36A, S16G/H19Y/T36A/N53D, S9P/N11D/S16G/H19Y/T36A/N47S/N53D, Q3P/S9P/H19Y/N31S/T36A/R39H/N47R/K50E, M1V/L2S/M4T/N11D/H19Y/T36A, M1V/L2S/M4T/N11D/T36A, M1V/L2S/M4T/H19Y/T36I/V45A/V49M, M1V/L2S/M4T/N11D/H19Y/T36A, M1V/L2S/M4T/S9P/Q10R/H19Y/T36A/T46A/N47S, M1V/L2S/M4T/S16G/N31D/T32I/T36A, M1V/M4T/T36A/Q38R/N53K, M1T/N11D/H19Y/T36A/N42S/V45A/N53S, M1T/N31D/T32A/T36A/A38R/S44D/V49A/K50E, M1T/S9P/P23S/Q38R/N42S/S48P/V49A/A54V, H19Y/T36A/S44G, H19Y/T36A, and M4T/T36A/Q38R/N42S/S44G/T46A/N47K/S48P/T52A.

22. The method according to any one of claims 1-18, wherein said variant sBCMA domain comprises the amino acid substitutions S16G/H19Y/T36A, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T,

M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

23. The method according to any one of claims 1-18, wherein said variant sBCMA domain comprises the amino acid substitutions S16G/H19Y/T36A/N53D, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53K, N53S, A54V, and A54T.

24. The method according to any one of claims 1-18, wherein said variant sBCMA domain comprises the amino acid substitutions S9P/N11D/S16G/H19Y/T36A/N47S/N53D, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, Q10H, Q10P, Q10R, N11S, E12K, F14L, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53K, N53S, A54V, and A54T.

25. The method according to any one of claims 1-18, wherein said variant sBCMA domain comprises the amino acid substitutions Q3P/S9P/H19Y/N31S/T36A/R39H/N47R/K50E, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16G, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, N42D, N42R,

N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47S, S48L, S48P, S48T, V49A, V49M, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

26. The method according to any one of claims 1-18, wherein said variant sBCMA domain comprises the amino acid substitutions M1V/L2S/M4T/S16G/N31D/T32I/T36A, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, L2C, Q3P, Q3R, M4E, M4I, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16N, S16R, H19L, H19Y, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31S, T32A, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

27. The method according to any one of claims 1-18, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 67.

28. The method according to any one of claims 1-18, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 68.

29. The method according to any one of claims 1-18, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 69.

30. The method according to any one of claims 1-18, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 49.

31. The method according to any one of claims 1-18, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 74.

32. The method according to any one of claims 1-18, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 67.

33. The method according to any one of claims 1-18, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 68.

34. The method according to any one of claims 1-18, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 69.

35. The method according to any one of claims 1-18, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 49.

36. The method according to any one of claims 1-18, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 74.

37. The method according to any one of the preceding claims, wherein said Fc domain is a human IgG Fc domain or a variant human IgG Fc domain.

38. The method according to claim 37, wherein said human IgG Fc domain comprises the hinge-CH2-CH3 of human IgG1.

39. The method according to claim 37, wherein said Fc domain is a variant human IgG Fc domain.

40. The method according to claim 37, wherein said Fc domain is a human IgG1 Fc domain.

41. The method according to any one of the preceding claims, wherein said linker is SEQ ID NO:87.

42. The method according to any one of claims 1-40, wherein said linker is selected from the group consisting of (GS)n, (GSGGS)n, (GGGGS)n, and (GGGS)n, wherein n is selected from the group consisting of 1, 2, 3, 4 and 5.

43. The method according to claim 42, wherein said linker is SEQ ID NO:88.

44. The method according to claim 1 or claim 2, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:80.

45. The method according to claim 1 or claim 2, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:81.

46. The method according to claim 1 or claim 2, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:82.

47. The method according to claim 1 or claim 2, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:83.

48. The method according to any one of claims 1-4, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:84.

FIGURE 1

Study Design

Group	Number of animals		Animal number		Treatment	Dose level	Concentration	Dose volume
	Male	Female	Male	Female		mg/kg	mg/mL	mL/kg
1	1	1	1101	2102	Vehicle	0	0	10
2	1	1	1203	2204	sBCMA V3	0.1	0.01	10
3	1	1	1305	2306	sBCMA V3	1	0.1	10
4	1	1	1407	2408	sBCMA V3	10	1	10
5	1	1	1509	2510	sBCMA V3	100	10	10

All dose levels/concentrations in the table are nominal.

Bodyweight Recorded:
Pre-dose: Days -14, -6
After dose: Days 1, 2, 7, 14, 21, 28, 35 and 42.
Blood Sample Collected:
Pre-dose: Days -13, -6, 1
After dose: Days 2, 7, 14, 42

FIGURE 2

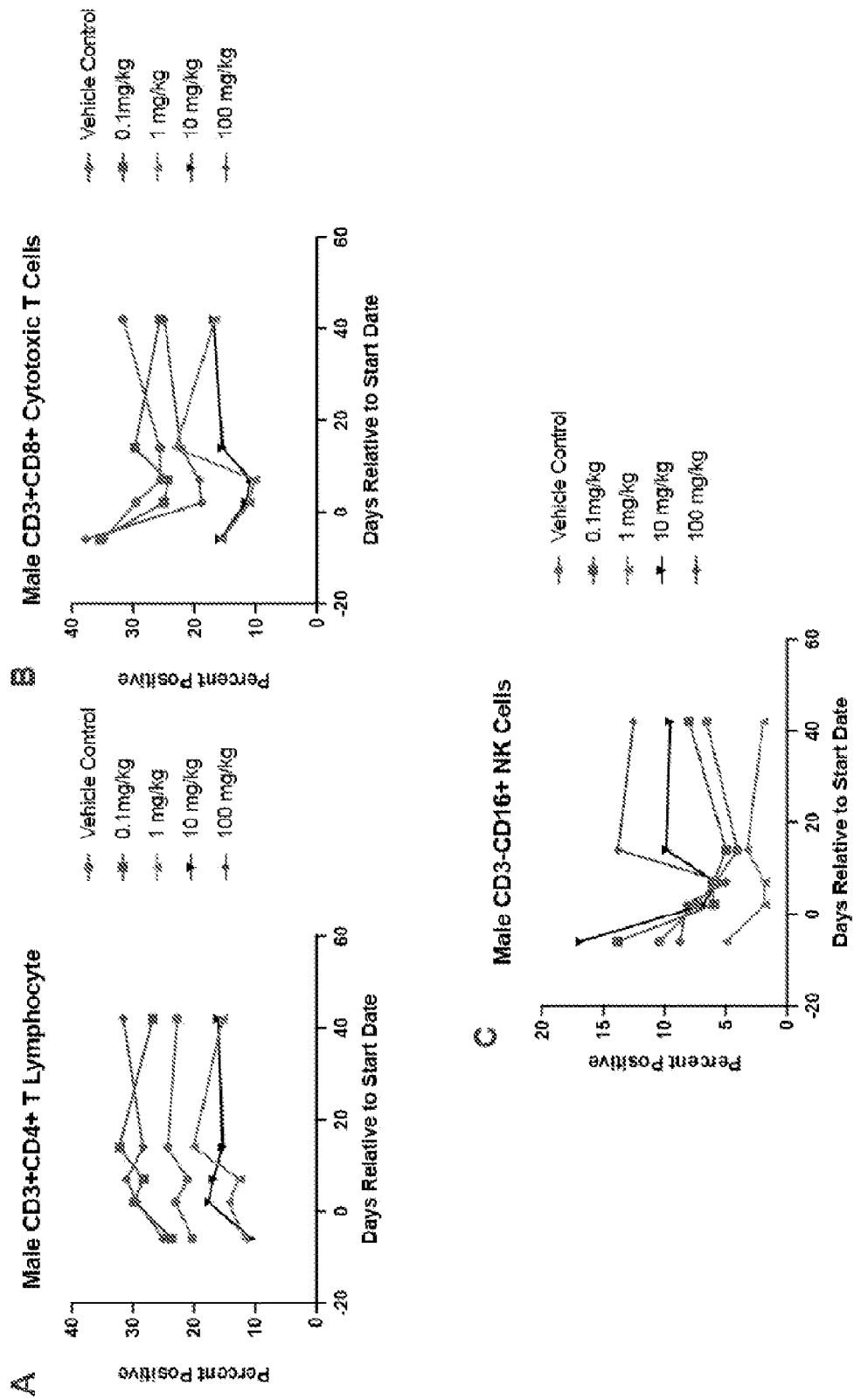

Male Cynomolgous Monkey Immune Cells Counts
A
Male CD3+CD4+ T Lymphocyte
Percent Positive
Days Relative to Start Date
B
Male CD3+CD8+ Cytotoxic T Cells
Percent Positive
Days Relative to Start Date
Vehicle Control
0.1mg/kg
1 mg/kg
10 mg/kg
100 mg/kg
C
Male CD3-CD16+ NK Cells
Percent Positive
Days Relative to Start Date
Vehicle Control
0.1mg/kg
1 mg/kg
10 mg/kg
100 mg/kg

FIGURE 2 - continued

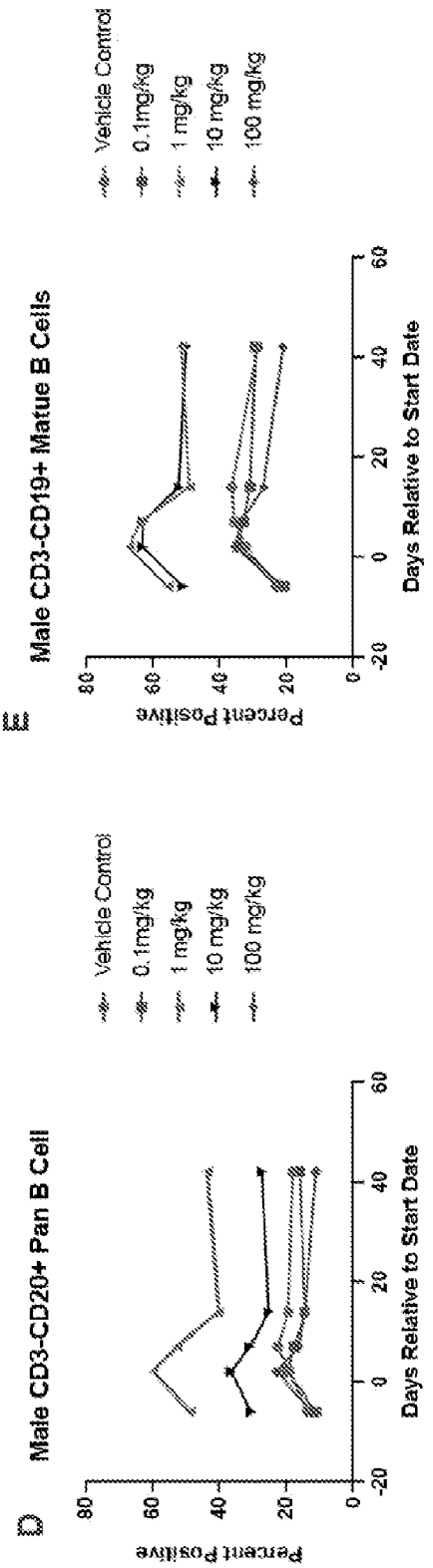


FIGURE 3

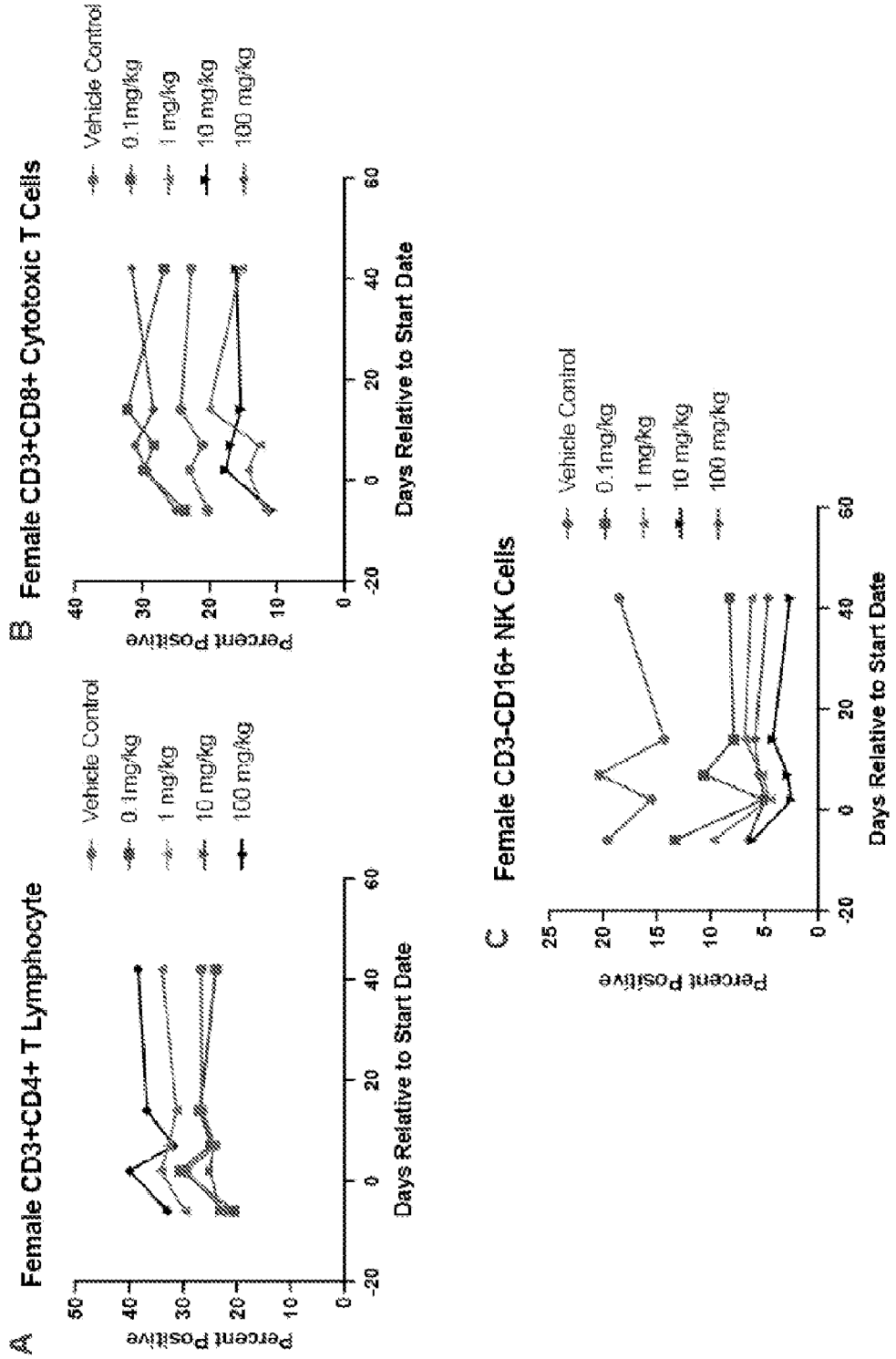

Female Cynomolgous Monkey Immune Cells Counts
A
Female CD3+CD4+ T Lymphocyte
Percent Positive
Days Relative to Start Date
Vehicle Control
0.1mg/kg
1 mg/kg
10 mg/kg
100 mg/kg
B
Female CD3+CD8+ Cytotoxic T Cells
Percent Positive
Days Relative to Start Date
Vehicle Control
0.1mg/kg
1 mg/kg
10 mg/kg
100 mg/kg
C
Female CD3-CD16+ NK Cells
Percent Positive
Days Relative to Start Date
Vehicle Control
0.1mg/kg
1 mg/kg
10 mg/kg
100 mg/kg

FIGURE 3 - continued

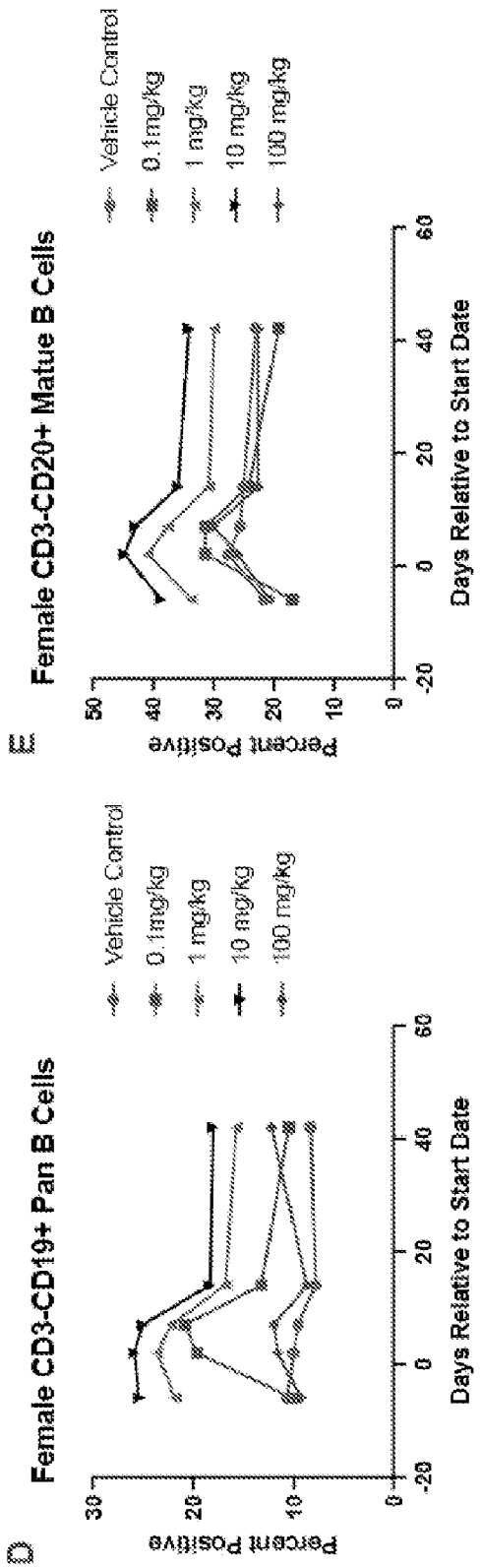


FIGURE 4

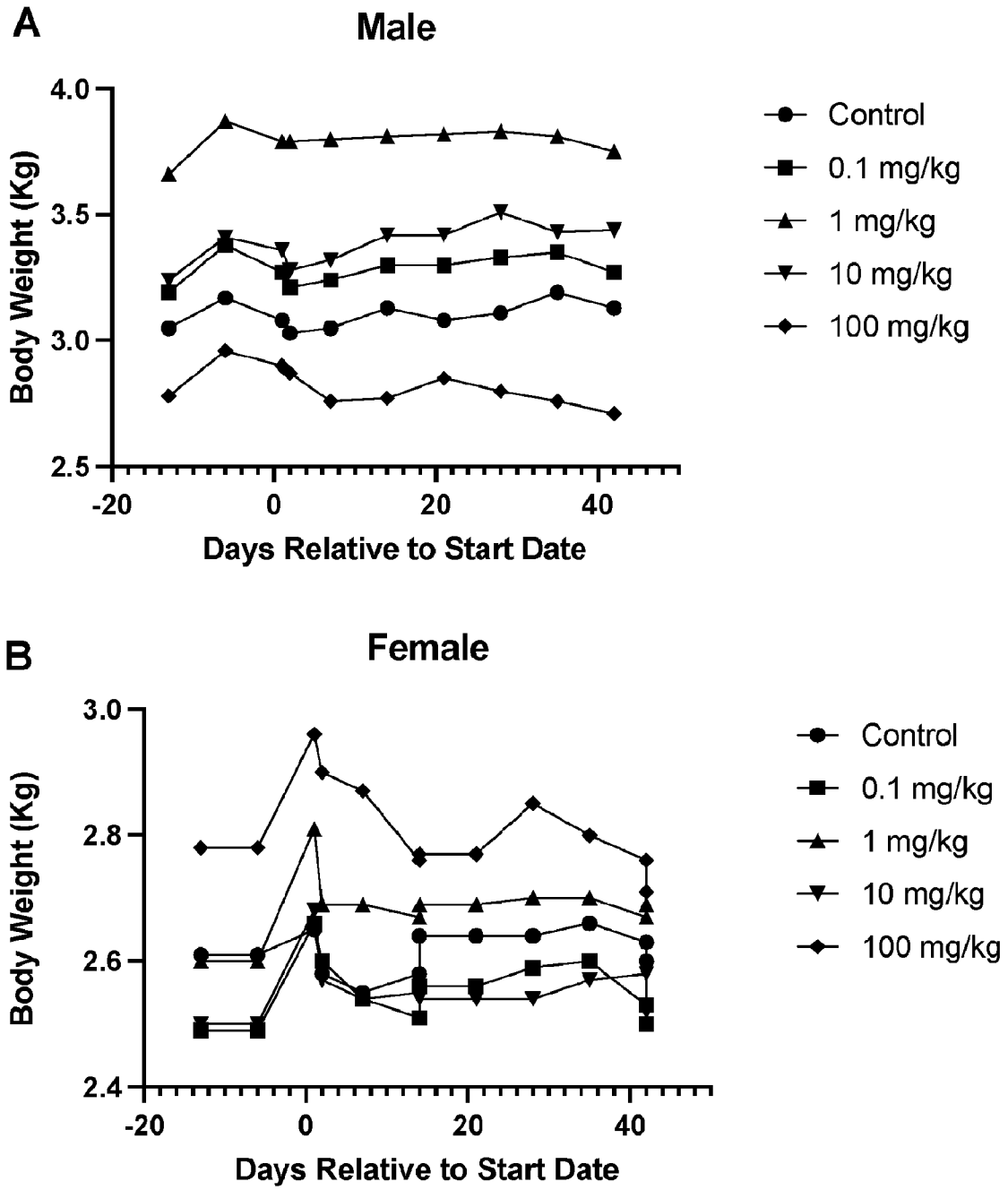

A
Male
Body Weight (Kg)
4.0
3.5
3.0
2.5
-20
0
20
40
Days Relative to Start Date
Control
0.1 mg/kg
1 mg/kg
10 mg/kg
100 mg/kg
B
Female
Body Weight (Kg)
3.0
2.8
2.6
2.4
-20
0
20
40
Days Relative to Start Date
Control
0.1 mg/kg
1 mg/kg
10 mg/kg
100 mg/kg

FIGURE 5

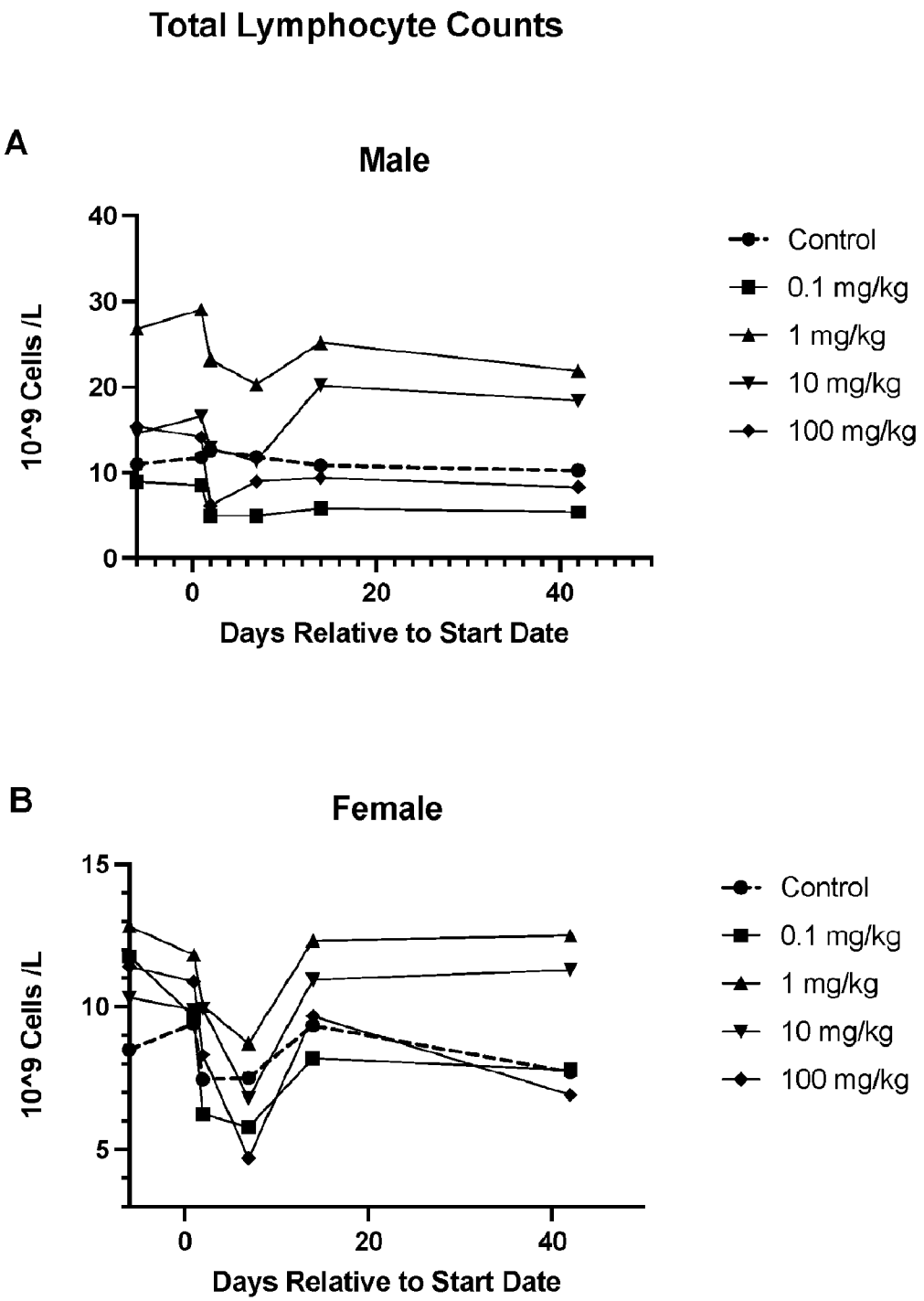

Total Lymphocyte Counts
A
Male
10^9 Cells /L
40
30
20
10
0
0
20
40
Days Relative to Start Date
Control
0.1 mg/kg
1 mg/kg
10 mg/kg
100 mg/kg
B
Female
10^9 Cells /L
15
10
5
0
20
40
Days Relative to Start Date
Control
0.1 mg/kg
1 mg/kg
10 mg/kg
100 mg/kg

FIGURE 6

Changes of Immunoglobulin in the Females at 1 to 100 mg/kg

Parameters	Animal Number	Dose Level (mg/kg)	Day -6	Day 2	Day 7	Day 14	Day 42
IgA (g/L)	2306	1	1.33	/	-20%	-35%	/
	2408	10	0.9	/	-30%	-50%	-61%
	2510	100	0.98	/	-27%	-52%	-87%
IgG (g/L)	2408	10	9.12	/	/	-22%	/
	2510	100	12.24	/	/	-25%	-37%
IgM (g/L)	2306	1	1.49	/	-24%	-40%	/
	2408	10	0.96	/	-32%	-43%	-51%
	2510	100	0.93	/	-20%	-42%	-74%

Formula: (Parameter Day n - Parameter Day -6)/ Parameter Day -6 ×100%. /: No abnormality.

FIGURE 7

Changes of Immunoglobulin in the Males at 1 to 100 mg/kg

Parameters	Animal Number	Dose Level (mg/kg)	Day -6	Day 2	Day 7	Day 14	Day 42
IgA (g/L)	1305	1	1	/	-19%	-44%	/
	1407	10	0.84	/	-18%	-31%	/
	1509	100	0.95	-20%	-37%	-54%	-75%
IgG (g/L)	1509	100	16.38	/	-34%	-44%	-56%
IgM (g/L)	1305	1	1.83	/	-24%	-38%	/
	1407	10	0.85	/	/	-25%	-29%
	1509	100	2.75	-38%	-56%	-70%	-82%

Formula: (Parameter Day n - Parameter Day -6)/ Parameter Day -6 ×100%. /: No abnormality.

FIGURE 8

Male Hematology Panel I

Vehicle Control	Day(s) Relative toStart Date	RBC (10^12/L)	HGB (g/L)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/L)	RDW (%)	RET (10^9/L)
1101	-13	6.21	139	49.4	79.6	22.4	281	13.3	192.0
	-6	5.89	133	47.4	80.6	22.6	280	13.1	121.0
	1	5.47	124	41.7	76.3	22.7	298	13.3	154.9
	2	5.29	119	43.7	82.5	22.5	273	13.4	198.3
	7	4.99	112	38.9	77.9	22.4	287	13.6	235.8
	14	5.42	124	40.5	74.6	22.8	305	13.3	169.3
	42	5.81	129	42.6	73.4	22.3	303	13.4	109.6

AB001 0.1 mg/kg	Day(s) Relative toStart Date	RBC (10^12/L)	HGB (g/L)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/L)	RDW (%)	RET (10^9/L)
1203	-13	5.61	126	43.5	77.6	22.4	289	13.5	209.8
	-6	6.23	140	47.9	76.8	22.5	293	12.9	140.6
	1	5.61	126	42.6	75.9	22.5	297	12.7	136.3
	2	5.12	114	39.0	76.2	22.3	292	12.9	157.0
	7	5.18	116	38.6	74.6	22.4	301	13.1	236.5
	14	5.55	122	40.2	72.4	22.0	304	12.9	178.4
	42	6.14	139	44.4	72.3	22.6	313	12.1	89.2

FIGURE 8 - continued

AB001 1 mg/kg	Day(s) Relative to Start Date	RBC (10^12/L)	HGB (g/L)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/L)	RDW (%)	RET (10^9/L)
1305	-13	6.18	137	45.6	73.8	22.1	300	12.9	250.0
	-6	6.55	147	47.7	72.9	22.5	309	12.3	160.5
	-3	6.69	151	47.9	71.6	22.5	315	12.2	137.3
	1	6.37	142	45.0	70.6	22.3	316	12.2	123.4
	2	5.67	127	41.3	72.8	22.4	307	12.4	144.8
	7	5.71	128	40.2	70.3	22.3	317	12.5	172.0
	14	6.08	132	42.7	70.2	21.8	310	12.2	188.3
	42	6.26	136	42.4	67.7	21.7	320	11.9	95.1

AB001 10 mg/kg	Day(s) Relative to Start Date	RBC (10^12/L)	HGB (g/L)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/L)	RDW (%)	RET (10^9/L)
1407	-13	5.00	115	38.1	76.1	22.9	301	13.8	232.6
	-6	5.55	128	43.9	79.1	23.1	292	13.1	149.8
	-3	5.27	121	39.1	74.3	22.9	308	12.7	170.4
	1	5.53	127	41.3	74.7	23.0	308	12.8	192.1
	2	5.02	114	37.9	75.5	22.7	301	13.1	193.8
	7	4.94	112	36.7	74.3	22.6	304	13.1	272.2
	14	5.22	118	38.9	74.5	22.5	302	12.9	250.5
	42	5.46	124	40.7	74.6	22.7	305	12.3	112.3

FIGURE 8 - continued

AB001 100 mg/kg	Day(s) Relative to Start Date	RBC (10^12/L)	HGB (g/L)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/L)	RDW (%)	RET (10^9/L)
1509	-13	6.12	137	46.9	76.5	22.3	291	12.6	100.6
	-6	6.21	136	45.9	73.9	21.8	295	12.7	116.1
	1	5.89	131	44.0	74.8	22.3	298	12.9	152.1
	2	5.56	121	42.6	76.6	21.7	284	13.1	141.4
	7	5.32	115	39.3	73.8	21.6	292	13.2	258.1
	14	5.94	128	46.4	78.1	21.6	276	12.9	220.7
	42	6.71	147	51.4	76.7	21.9	285	12.6	88.2

Abbreviations:

RBC	Red Blood Cells
HGB	Hemoglobin
HCT	Hematocrit
MCV	Mean Corpuscular Volume
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
RDW	Red Cell Distribution Width
RET	Reticulocytes (Absolute)

FIGURE 9

Male Hematology II

Vehicle Control	Day(s) Relative to Start Date	PLT (10^9/L)	WBC (10^9/L)	NEUT (10^9/L)	LYMP (10^9/L)	MONO (10^9/L)	EOS (10^9/L)	BASO (10^9/L)
1101	-13	257	16.07	8.51	6.91	0.24	0.17	0.11
	-6	297	18.52	5.88	10.99	0.47	0.83	0.16
	1	295	21.84	8.67	11.78	0.45	0.60	0.14
	2	270	21.24	7.36	12.58	0.41	0.49	0.18
	7	327	18.12	5.08	11.85	0.43	0.50	0.11
	14	386	20.46	8.21	10.86	0.43	0.63	0.16
	42	280	15.70	4.30	10.26	0.38	0.47	0.12

AB001 0.1 mg/kg	Day(s) Relative to Start Date	PLT (10^9/L)	WBC (10^9/L)	NEUT (10^9/L)	LYMP (10^9/L)	MONO (10^9/L)	EOS (10^9/L)	BASO (10^9/L)
1203	-13	347	9.14	4.36	4.32	0.30	0.07	0.04
	-6	436	11.74	1.82	8.93	0.49	0.30	0.11
	1	387	10.69	1.43	8.52	0.26	0.34	0.07
	2	369	11.81	6.25	4.95	0.37	0.14	0.05
	7	410	9.25	3.78	4.95	0.24	0.19	0.04
	14	436	8.93	2.54	5.80	0.27	0.25	0.03
	42	364	12.90	6.83	5.37	0.38	0.19	0.07

FIGURE 9 - continued

AB001 1 mg/kg	Day(s) Relative to Start Date	PLT (10^9/L)	WBC (10^9/L)	NEUT (10^9/L)	LYMP (10^9/L)	MONO (10^9/L)	EOS (10^9/L)	BASO (10^9/L)
1305	-13	334	22.46	6.80	14.83	0.32	0.05	0.20
	-6	375	36.24	7.27	26.77	0.72	0.33	0.54
	-3	335	30.61	4.56	24.24	0.44	0.37	0.47
	1	386	35.27	4.59	29.04	0.25	0.31	0.56
	2	330	32.46	7.99	23.17	0.29	0.26	0.38
	7	356	33.46	11.88	20.27	0.33	0.28	0.38
	14	343	34.98	8.03	25.17	0.45	0.47	0.43
	42	306	28.18	4.86	21.89	0.49	0.22	0.32

AB001 10 mg/kg	Day(s) Relative to Start Date	PLT (10^9/L)	WBC (10^9/L)	NEUT (10^9/L)	LYMP (10^9/L)	MONO (10^9/L)	EOS (10^9/L)	BASO (10^9/L)
1407	-13	375	14.70	4.79	9.52	0.18	0.05	0.09
	-6	389	30.01	13.65	14.59	1.07	0.25	0.26
	-3	382	16.90	1.49	14.57	0.37	0.18	0.16
	1	339	19.36	1.85	16.55	0.36	0.25	0.19
	2	302	17.83	4.11	12.91	0.29	0.21	0.16
	7	375	16.53	4.47	11.34	0.31	0.22	0.11
	14	443	26.94	5.32	20.19	0.50	0.41	0.30
	42	331	22.21	2.61	18.37	0.46	0.29	0.25

FIGURE 9 - continued

AB001 100 mg/kg	Day(s) Relative to Start Date	PLT (10^9/L)	WBC (10^9/L)	NEUT (10^9/L)	LYMP (10^9/L)	MONO (10^9/L)	EOS (10^9/L)	BASO (10^9/L)
1509	-13	452	10.38	5.67	3.82	0.70	0.03	0.09
	-6	494	25.43	8.46	15.40	0.65	0.25	0.36
	1	515	20.92	5.45	14.11	0.58	0.37	0.21
	2	457	33.35	25.95	6.15	0.93	0.10	0.15
	7	409	18.22	8.40	8.97	0.47	0.13	0.14
	14	599	20.36	10.09	9.39	0.45	0.19	0.15
	42	510	16.62	7.42	8.33	0.52	0.14	0.12

Abbreviations:

PLT	Platelets
WBC	White Blood Cells
NEUT	Neutrophils (Absolute)
LYMP	Lymphocytes (Absolute)
MONO	Monocytes (Absolute)
EOS	Eosinophils (Absolute)
BASO	Basophils (Absolute)

FIGURE 10

Female Hematology I

Vehicle Control	Day(s) Relative to Start Date	RBC (10^12/L)	HGB (g/L)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/L)	RDW (%)	RET (10^9/L)
2102	-13	6.31	141	46.3	73.4	22.4	305	12.4	122.8
	-6	6.75	148	49.8	73.9	21.9	296	11.9	114.0
	1	6.00	131	44.2	73.7	21.9	297	12.0	121.5
	2	5.32	116	39.0	73.3	21.7	296	12.2	117.1
	7	5.45	119	41.0	75.2	21.8	290	12.5	255.5
	14	5.77	126	42.0	72.8	21.8	300	12.2	196.7
	42	6.18	136	44.3	71.7	22.1	308	11.5	72.4

AB001 0.1 mg/kg	Day(s) Relative to Start Date	RBC (10^12/L)	HGB (g/L)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/L)	RDW (%)	RET (10^9/L)
2204	-13	5.15	129	42.2	82.1	25.0	305	14.4	99.3
	-6	5.31	136	43.1	81.1	25.5	315	14.3	101.3
	1	4.90	127	40.1	81.7	25.9	317	14.2	95.9
	2	4.60	113	37.0	80.4	24.6	306	14.4	107.8
	7	4.59	114	36.9	80.5	24.8	308	14.3	238.0
	14	4.95	123	39.6	80.0	24.8	310	14.3	180.1
	42	5.47	135	43.2	79.0	24.7	313	13.6	99.0

FIGURE 10 - continued

AB001 1 mg/kg	Day(s) Relative to Start Date	RBC (10^12/L)	HGB (g/L)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/L)	RDW (%)	RET (10^9/L)
2306	-13	5.20	125	40.9	78.6	24.0	306	13.1	70.8
	-6	5.06	123	40.1	79.2	24.4	308	13.0	77.4
	1	4.98	121	39.8	79.8	24.3	305	13.1	80.4
	2	4.48	108	35.4	78.9	24.1	305	13.3	74.3
	7	4.55	111	35.8	78.6	24.3	309	13.6	148.8
	14	4.97	121	38.9	78.4	24.3	311	13.1	97.7
	42	5.25	130	40.1	76.4	24.7	323	12.2	40.1

AB001 10 mg/kg	Day(s) Relative to Start Date	RBC (10^12/L)	HGB (g/L)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/L)	RDW (%)	RET (10^9/L)
2408	-13	5.23	128	40.9	78.3	24.4	312	12.1	77.8
	-6	5.30	129	42.4	80.1	24.3	303	11.8	90.7
	1	5.08	126	39.7	78.2	24.9	318	12.2	84.3
	2	4.70	115	37.1	79.0	24.5	310	12.2	97.1
	7	4.50	109	34.8	77.4	24.3	314	12.4	177.5
	14	4.85	117	37.0	76.2	24.1	316	11.9	91.4
	42	5.28	131	39.7	75.2	24.7	329	11.5	46.0

FIGURE 10 - continued

AB001 100 mg/kg	Day(s) Relative to Start Date	RBC (10^12/L)	HGB (g/L)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/L)	RDW (%)	RET (10^9/L)
2510	-13	5.25	112	37.9	72.3	21.3	295	14.6	152.9
	-6	5.42	113	38.9	71.8	20.9	291	14.0	141.6
	1	5.18	109	37.0	71.6	21.1	295	14.1	143.2
	2	4.67	97	34.5	73.9	20.8	282	14.1	141.3
	7	4.84	103	34.0	70.2	21.2	302	14.5	194.5
	14	5.10	108	36.5	71.5	21.1	295	14.1	197.4
	42	5.40	114	36.9	68.3	21.1	309	12.9	100.6

Abbreviations:

RBC	Red Blood Cells
HGB	Hemoglobin
HCT	Hematocrit
MCV	Mean Corpuscular Volume
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
RDW	Red Cell Distribution Width
RET	Reticulocytes (Absolute)

FIGURE 11

Female Hematology II

Vehicle Control	Day(s) Relative to Start Date	PLT (10^9/_)	WBC (10^9/L)	NEUT (10^9/L)	LYMP (10^9/L)	MONO (10^9/L)	EOS (10^9/L)	BASO (10^9/L)
2102	-13	409	12.30	8.25	3.64	0.28	0.01	0.06
	-6	465	17.31	7.58	8.49	0.71	0.26	0.13
	1	463	17.06	6.68	9.41	0.47	0.21	0.13
	2	401	19.30	10.82	7.45	0.65	0.16	0.09
	7	466	18.84	10.43	7.52	0.53	0.14	0.10
	14	498	22.49	11.69	9.34	0.80	0.30	0.17
	42	406	15.61	6.94	7.72	0.55	0.18	0.11

AB001 0.1 mg/kg	Day(s) Relative to Start Date	PLT (10^9/L)	WBC (10^9/L)	NEUT (10^9/L)	LYMP (10^9/L)	MONO (10^9/L)	EOS (10^9/L)	BASO (10^9/L)
2204	-13	291	10.33	5.08	4.84	0.29	0.02	0.05
	-6	336	17.92	4.68	11.78	0.85	0.26	0.19
	1	314	15.43	4.61	9.67	0.66	0.24	0.13
	2	299	12.04	5.17	6.24	0.33	0.15	0.07
	7	371	12.08	5.61	5.78	0.43	0.11	0.08
	14	343	15.24	5.98	8.20	0.66	0.18	0.11
	42	292	13.39	4.75	7.79	0.47	0.19	0.08

FIGURE 11 - continued

AB001 1 mg/kg	Day(s) Relative to Start Date	PLT (10^9/L)	WBC (10^9/L)	NEUT (10^9/L)	LYMP (10^9/L)	MONO (10^9/L)	EOS (10^9/L)	BASO (10^9/L)
2306	-13	511	18.73	12.88	5.48	0.23	0.04	0.06
	-6	459	19.87	6.05	12.81	0.52	0.19	0.17
	1	551	16.10	3.61	11.82	0.26	0.21	0.10
	2	464	22.11	11.37	10.04	0.38	0.13	0.11
	7	468	16.55	7.28	8.71	0.32	0.10	0.08
	14	462	19.52	6.17	12.31	0.47	0.31	0.15
	42	426	19.46	6.04	12.49	0.39	0.28	0.16

AB001 10 mg/kg	Day(s) Relative to Start Date	PLT (10^9/L)	WBC (10^9/L)	NEUT (10^9/L)	LYMP (10^9/L)	MONO (10^9/L)	EOS (10^9/L)	BASO (10^9/L)
2408	-13	283	11.59	4.41	6.73	0.30	0.02	0.05
	-6	304	17.57	6.30	10.31	0.44	0.20	0.17
	1	324	14.88	3.99	9.90	0.42	0.33	0.10
	2	297	18.24	7.51	9.92	0.42	0.17	0.10
	7	294	17.57	10.20	6.80	0.32	0.10	0.08
	14	307	17.15	5.12	10.95	0.58	0.29	0.10
	42	300	21.70	9.11	11.29	0.74	0.22	0.15

FIGURE 11 - continued

AB001 100 mg/kg	Day(s) Relative to Start Date	PLT (10^9/L)	WBC (10^9/L)	NEUT (10^9/L)	LYMP (10^9/L)	MONO (10^9/L)	EOS (10^9/L)	BASO (10^9/L)
2510	-13	359	13.64	7.64	5.45	0.36	0.07	0.06
	-6	452	21.25	8.50	11.41	0.55	0.51	0.14
	1	418	18.34	6.48	10.88	0.40	0.38	0.09
	2	389	19.60	10.71	8.31	0.28	0.13	0.08
	7	434	18.73	13.53	4.70	0.22	0.17	0.04
	14	433	20.69	10.11	9.67	0.31	0.35	0.11
	42	412	20.23	12.52	6.91	0.35	0.28	0.11

Abbreviations:

PLT	Platelets
WBC	White Blood Cells
NEUT	Neutrophils (Absolute)
LYMP	Lymphocytes (Absolute)
MONO	Monocytes (Absolute)
EOS	Eosinophils (Absolute)
BASO	Basophils (Absolute)

FIGURE 12

Male Coagulation

Vehicl eContr ol	Day(s) Relative toStart Date	PT (Seconds)	APTT (Seconds)	FIB (g/L)
1101	-13	10.8	16.7	2.03
	-6	9.8	16.6	1.61
	2	9.8	16.7	2.22
	42	9.8	16.3	1.80

AB001 0.1 mg/kg	Day(s) Relative toStart Date	PT (Seconds)	APTT (Seconds)	FIB (g/L)
1203	-13	9.8	18.7	1.84
	-6	9.0	20.1	1.80
	2	9.1	18.5	2.17
	42	8.6	19.7	2.07

AB001 1 mg/kg	Day(s) Relative toStart Date	PT (Seconds)	APTT (Seconds)	FIB (g/L)
1305	-13	10.7	18.6	2.65
	-6	9.5	19.0	2.49
	2	9.6	18.9	2.78
	42	9.4	20.0	3.54

AB001 10 mg/kg	Day(s) Relative toStart Date	PT (Seconds)	APTT (Seconds)	FIB (g/L)
1407	-13	9.3	16.9	2.53
	-6	9.1	17.7	2.65
	2	9.1	16.8	2.78
	42	9.0	18.1	2.61

FIGURE 12 - continued

AB001 100 mg/kg	Day(s) Relative toStart Date	PT (Seconds)	APTT (Seconds)	FIB (g/L)
1509	-13	11.5	20.4	2.74
	-6	10.2	19.4	2.11
	2	11.1	19.6	4.02
	42	10.6	19.8	2.31

Abbreviations:

PT	Prothrombin Time
APTT	Activated Partial Thromboplastin Time
FIB	Fibrinogen

FIGURE 13

Female Coagulation

Vehicle Control	Day(s) Relative toStart Date	PT (Seconds)	APTT (Seconds)	FIB (g/L)
2102	-13	10.8	17.4	2.19
	-6	9.9	16.7	2.03
	2	10.1	17.6	2.93
	42	9.8	18.3	2.20

AB001 0.1 mg/kg	Day(s) Relative toStart Date	PT (Seconds)	APTT (Seconds)	FIB (g/L)
2204	-13	10.2	16.8	2.35
	-6	9.3	16.9	2.39
	2	9.4	17.5	2.93
	42	9.2	18.1	2.54

AB001 1 mg/kg	Day(s) Relative toStart Date	PT (Seconds)	APTT (Seconds)	FIB (g/L)
2306	-13	9.3	15.9	2.32
	-6	8.8	14.6	2.03
	2	9.3	15.7	2.57
	42	8.5	14.8	2.15

AB001 10 mg/kg	Day(s) Relative toStart Date	PT (Seconds)	APTT (Seconds)	FIB (g/L)
2408	-13	10.6	18.2	1.93
	-6	9.0	17.3	1.95
	2	9.2	17.9	2.11
	42	8.8	18.6	2.34

FIGURE 13 - continued

AB001 100 mg/kg	Day(s) Relative toStart Date	PT (Seconds)	APTT (Seconds)	FIB (g/L)
2510	-13	10.2	19.9	1.86
	-6	9.5	19.1	1.80
	2	9.2	20.0	2.11
	42	9.3	17.4	2.26

Abbreviations:

PT	Prothrombin Time
APTT	Activated Partial Thromboplastin Time
FIB	Fibrinogen

FIGURE 14

Male Chemistry I

Vehicle Control	Day(s) Relative toStart Date	ALT (U/L)	AST (U/L)	ALP (U/L)	GGT (U/L)	CK (U/L)	TBIL (μmol/L)	GLU (mmol/L)
1101	-13	32.9	45.5	1122	61	175	5.9	3.63
	-6	20.7	32.0	897	54	222	2.5	7.07
	2	34.3	72.3	766	53	221	2.5	6.21
	7	24.5	33.8	749	49	143	1.8	6.03
	14	19.2	27.6	783	49	195	0.7	6.96
	42	20.9	32.3	946	59	142	2.1	5.51

AB001 0.1 mg/kg	Day(s) Relative toStart Date	ALT (U/L)	AST (U/L)	ALP (U/L)	GGT (U/L)	CK (U/L)	TBIL (μmol/L)	GLU (mmol/L)
1203	-13	49.9	72.3	799	95	302	3.1	5.77
	-6	28.0	39.9	745	84	505	1.5	7.41
	2	54.8	93.5	702	77	715	1.6	5.92
	7	29.7	38.1	747	71	210	0.6	6.44
	14	26.0	37.2	803	74	318	0.6	5.12
	42	24.8	40.3	862	77	326	0.8	6.15

AB001 1 mg/kg	Day(s) Relative toStart Date	ALT (U/L)	AST (U/L)	ALP (U/L)	GGT (U/L)	CK (U/L)	TBIL (μmol/L)	GLU (mmol/L)
1305	-13	42.2	55.5	681	140	472	5.4	5.68
	-6	28.7	37.2	534	106	313	3.0	6.84
	2	43.9	75.8	513	97	753	2.7	6.00
	7	63.4	60.0	508	90	745	2.6	5.34
	14	31.8	32.4	531	93	213	1.1	5.77
	42	23.1	34.6	529	89	295	2.6	6.17

FIGURE 14 - conitnued

AB001 10 mg/kg	Day(s) Relative toStart Date	ALT (U/L)	AST (U/L)	ALP (U/L)	GGT (U/L)	CK (U/L)	TBIL (μmol /L)	GLU (mmol /L)
1407	-13	64.6	71.1	601	87	664	3.2	6.84
	-6	62.7	51.4	565	87	416	2.6	6.50
	2	61.0	108.5	525	76	471	2.0	6.83
	7	51.4	51.4	490	70	359	2.3	6.30
	14	42.8	38.4	501	72	234	1.2	5.83
	42	38.7	38.8	569	82	257	1.8	6.97

AB001 100 mg/kg	Day(s) Relative toStart Date	ALT (U/L)	AST (U/L)	ALP (U/L)	GGT (U/L)	CK (U/L)	TBIL (μmol /L)	GLU (mmol /L)
1509	-13	92.7	71.8	613	80	188	3.2	5.62
	-6	55.7	34.4	499	69	184	1.4	7.21
	2	257.8	866.5	581	82	1213 5	2.9	7.19
	7	272.2	117.9	593	71	614	1.4	6.76
	14	86.2	44.8	680	83	179	0.7	7.43
	42	60.3	46.1	827	98	281	1.5	7.82

Abbreviations:

ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ALP	Alkaline Phosphatase
GGT	Gamma Glutamyl Transferase
CK	Creatine Kinase
TBIL	Total Bilirubin
GLU	Glucose

FIGURE 15

Male Chemistry II

Vehicle Control	Day(s) Relative toStart Date	UREA (mmol/L)	CREA (μmol/L)	TG (mmol/L)	CHOL (mmol/L)	TP (g/L)	ALB (g/L)	GLOB (g/L)
1101	-13	8.6	68	0.44	3.61	81.7	45.2	36.5
	-6	8.4	62	0.36	3.58	74.0	42.1	31.9
	2	8.2	64	0.32	3.33	73.3	42.4	30.9
	7	7.9	64	0.50	3.73	73.6	41.4	32.2
	14	8.8	66	0.42	3.92	72.5	40.8	31.7
	42	7.6	61	0.56	3.35	75.9	43.2	32.7

AB001 0.1 mg/kg	Day(s) Relative toStart Date	UREA (mmol/L)	CREA (μmol/L)	TG (mmol/L)	CHOL (mmol/L)	TP (g/L)	ALB (g/L)	GLOB (g/L)
1203	-13	8.3	69	0.63	2.95	74.1	46.5	27.6
	-6	7.7	63	0.71	3.59	75.0	45.0	30.0
	2	5.5	63	0.53	2.75	73.2	45.8	27.4
	7	6.9	67	0.52	3.07	73.8	44.9	28.9
	14	7.5	71	0.59	3.20	70.4	42.9	27.5
	42	7.2	69	1.09	3.41	75.0	46.0	29.0

AB001 1 mg/kg	Day(s) Relative toStart Date	UREA (mmol/L)	CREA (μmol/L)	TG (mmol/L)	CHOL (mmol/L)	TP (g/L)	ALB (g/L)	GLOB (g/L)
1305	-13	7.0	67	0.35	3.33	82.8	48.4	34.4
	-6	5.5	56	0.22	4.11	78.4	45.6	32.8
	2	5.1	59	0.26	3.29	78.5	45.5	33.0
	7	5.7	61	0.30	3.78	79.4	47.3	32.1
	14	5.5	60	0.22	4.05	76.4	46.0	30.4
	42	5.8	59	0.39	4.42	81.0	45.6	35.4

FIGURE 15 - continued

AB001 10 mg/kg	Day(s) Relative toStart Date	UREA (mmol/L)	CREA (μmol/L)	TG (mmol/L)	CHOL (mmol/L)	TP (g/L)	ALB (g/L)	GLOB (g/L)
1407	-13	7.4	69	0.46	3.50	76.6	44.1	32.5
	-6	6.5	65	0.98	3.84	79.6	45.6	34.0
	2	5.4	70	0.49	3.66	77.6	43.8	33.8
	7	6.3	74	0.39	3.62	75.7	45.1	30.6
	14	6.0	67	0.43	4.12	73.7	44.2	29.5
	42	6.2	74	1.20	3.94	74.5	44.9	29.6

AB001 100 mg/kg	Day(s) Relative toStart Date	UREA (mmol/L)	CREA (μmol/L)	TG (mmol/L)	CHOL (mmol/L)	TP (g/L)	ALB (g/L)	GLOB (g/L)
1509	-13	6.5	72	0.35	3.64	89.9	42.8	47.1
	-6	6.3	73	0.65	3.67	86.5	40.0	46.5
	2	6.0	71	0.44	3.11	83.3	42.0	41.3
	7	6.0	73	0.59	3.26	78.9	43.3	35.6
	14	6.4	70	0.48	4.20	77.8	45.5	32.3
	42	6.2	76	0.87	4.38	75.2	47.8	27.4

Abbreviations:

UREA	Urea
CREA	Creatinine
TG	Triglycerides
CHOL	Total Cholesterol
TP	Total Protein
ALB	Albumin
GLOB	Globulin

FIGURE 16

Male Chemistry III

Vehicle Control	Day(s) Relative toStart Date	A/G	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	IgA (g/L)	IgG (g/L)	IgM (g/L)
1101	-13	1.2	153	4.45	108.3	1.69	11.96	0.76
	-6	1.3	153	3.74	104.0	1.54	10.08	0.66
	2	1.4	154	4.14	108.1	1.43	9.25	0.59
	7	1.3	150	3.59	105.5	1.50	10.29	0.54
	14	1.3	148	4.04	106.3	1.46	9.80	0.54
	42	1.3	146	3.41	104.0	1.57	11.28	0.66

AB001 0.1 mg/kg	Day(s) Relative toStart Date	A/G	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	IgA (g/L)	IgG (g/L)	IgM (g/L)
1203	-13	1.7	156	4.20	112.4	0.81	8.44	0.51
	-6	1.5	155	5.03	106.7	0.93	8.27	0.63
	2	1.7	150	3.87	106.0	0.84	7.48	0.56
	7	1.6	150	3.82	106.8	0.86	7.41	0.52
	14	1.6	149	3.87	108.0	0.93	7.88	0.57
	42	1.6	147	3.58	104.7	1.09	9.06	0.64

AB001 1 mg/kg	Day(s) Relative toStart Date	A/G	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	IgA (g/L)	IgG (g/L)	IgM (g/L)
1305	-13	1.4	155	4.52	111.5	0.95	11.38	1.49
	-6	1.4	149	4.15	104.7	1.00	10.83	1.83
	2	1.4	148	3.81	106.0	0.91	10.62	1.69
	7	1.5	149	4.26	106.5	0.81	9.67	1.39
	14	1.5	149	4.01	106.7	0.56	8.91	1.13
	42	1.3	144	3.67	102.8	0.88	11.94	1.57

FIGURE 16 - continued

AB001 10 mg/kg	Day(s) Relative to Start Date	A/G	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	IgA (g/L)	IgG (g/L)	IgM (g/L)
1407	-13	1.4	152	4.08	108.0	0.75	10.20	0.74
	-6	1.3	152	3.60	103.1	0.84	9.93	0.85
	2	1.3	148	3.41	106.0	0.84	9.47	0.83
	7	1.5	147	3.49	105.8	0.69	8.96	0.74
	14	1.5	145	3.75	102.3	0.58	8.21	0.64
	42	1.5	146	3.07	98.7	0.66	9.34	0.60

AB001 100 mg/kg	Day(s) Relative to Start Date	A/G	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	IgA (g/L)	IgG (g/L)	IgM (g/L)
1509	-13	0.9	155	4.72	106.1	1.03	17.31	1.65
	-6	0.9	148	4.46	102.1	0.95	16.38	2.75
	2	1.0	150	4.51	103.9	0.76	14.11	1.70
	7	1.2	152	4.68	106.9	0.60	10.86	1.20
	14	1.4	153	5.03	104.6	0.44	9.21	0.82
	42	1.7	155	5.04	104.2	0.24	7.24	0.49

Abbreviations:

A/G	Albumin/Globulin Ratio
Na	Sodium
K	Potassium Chloride
Cl	Chloride
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M

FIGURE 17

Female Chemistry I

Vehicle Control	Day(s) Relative to Start Date	ALT (U/L)	AST (U/L)	ALP (U/L)	GGT (U/L)	CK (U/L)	TBIL (μmol/L)	GLU (mmol/L)
2102	-13	17.9	53.3	865	64	225	3.1	3.92
	-6	11.5	36.3	715	57	270	1.7	7.15
	2	29.2	208.0	688	50	3564	1.0	5.01
	7	58.2	55.1	623	50	218	0.8	6.95
	14	14.4	35.4	718	52	201	0.4	7.58
	42	10.7	41.9	708	56	144	1.2	5.53

AB001 0.1 mg/kg	Day(s) Relative to Start Date	ALT (U/L)	AST (U/L)	ALP (U/L)	GGT (U/L)	CK (U/L)	TBIL (μmol/L)	GLU (mmol/L)
2204	-13	43.0	49.3	365	55	225	3.1	3.67
	-6	28.5	28.3	344	57	153	1.5	5.76
	2	52.6	91.0	330	54	803	1.8	5.47
	7	82.2	62.8	320	54	508	1.6	5.54
	14	33.9	31.4	353	56	185	0.7	5.01
	42	30.1	38.1	406	61	203	1.6	6.41

AB001 1 mg/kg	Day(s) Relative to Start Date	ALT (U/L)	AST (U/L)	ALP (U/L)	GGT (U/L)	CK (U/L)	TBIL (μmol/L)	GLU (mmol/L)
2306	-13	41.1	60.4	404	80	715	3.5	4.90
	-6	28.5	30.5	326	79	158	2.2	5.32
	2	52.8	94.5	320	80	753	1.0	6.12
	7	39.5	37.3	319	77	217	1.5	4.76
	14	31.2	32.5	332	81	170	1.0	5.82
	42	25.7	35.9	403	92	164	1.2	5.14

FIGURE 17 - continued

AB001 10 mg/kg	Day(s) Relative to Start Date	ALT (U/L)	AST (U/L)	ALP (U/L)	GGT (U/L)	CK (U/L)	TBIL (μmol/L)	GLU (mmol/L)
2408	-13	53.1	71.0	680	56	394	4.2	4.50
	-6	44.7	39.3	581	54	257	2.8	6.27
	2	51.2	71.7	562	54	331	2.6	7.90
	7	36.6	34.9	527	53	158	2.3	5.80
	14	40.7	33.8	524	55	166	1.8	6.63
	42	33.7	39.6	706	57	233	2.1	4.41

AB001 100 mg/kg	Day(s) Relative to Start Date	ALT (U/L)	AST (U/L)	ALP (U/L)	GGT (U/L)	CK (U/L)	TBIL (μmol/L)	GLU (mmol/L)
2510	-13	29.7	62.0	397	67	154	3.2	5.88
	-6	16.4	31.0	328	62	106	1.8	7.48
	2	21.8	81.9	360	62	153	0.9	7.50
	7	22.9	38.6	331	62	109	1.0	6.71
	14	19.0	36.0	331	62	123	0.9	7.36
	42	15.8	33.2	372	61	132	1.5	6.38

Abbreviations:

ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ALP	Alkaline Phosphatase
GGT	Gamma Glutamyl Transferase
CK	Creatine Kinase
TBIL	Total Bilirubin
GLU	Glucose

FIGURE 18

Female Chemistry II

Vehicle Control	Day(s) Relative toStart Date	UREA (mmol/L)	CREA (μmol/L)	TG (mmol/L)	CHOL (mmol/L)	TP (g/L)	ALB (g/L)	GLOB (g/L)
2102	-13	7.4	37	0.49	2.47	78.1	45.4	32.7
	-6	7.2	44	0.40	2.30	73.1	43.2	29.9
	2	5.6	36	0.29	2.07	69.2	40.5	28.7
	7	5.2	37	0.22	2.34	69.3	41.2	28.1
	14	6.0	35	0.30	2.72	70.2	40.7	29.5
	42	5.3	36	0.59	2.50	71.6	43.5	28.1

AB001 0.1 mg/kg	Day(s) Relative toStart Date	UREA (mmol/L)	CREA (μmol/L)	TG (mmol/L)	CHOL (mmol/L)	TP (g/L)	ALB (g/L)	GLOB (g/L)
2204	-13	6.3	63	0.47	3.23	79.8	42.4	37.4
	-6	6.9	59	0.78	3.38	76.6	42.2	34.4
	2	5.2	63	0.44	3.18	73.1	38.8	34.3
	7	6.9	63	0.58	3.40	78.0	42.2	35.8
	14	6.6	61	0.46	3.71	74.6	39.9	34.7
	42	7.4	65	0.88	3.50	79.5	44.4	35.1

AB001 1 mg/kg	Day(s) Relative toStart Date	UREA (mmol/L)	CREA (μmol/L)	TG (mmol/L)	CHOL (mmol/L)	TP (g/L)	ALB (g/L)	GLOB (g/L)
2306	-13	5.9	54	0.38	3.69	79.5	43.7	35.8
	-6	5.6	52	0.29	3.82	75.2	41.5	33.7
	2	4.9	49	0.19	3.42	75.6	43.1	32.5
	7	5.0	55	0.21	3.96	74.1	44.6	29.5
	14	5.8	50	0.24	4.42	73.4	43.7	29.7
	42	5.6	48	0.32	4.28	75.2	44.1	31.1

FIGURE 18 - continued

AB001 10 mg/kg	Day(s) Relative toStart Date	UREA (mmol/L)	CREA (μmol/L)	TG (mmol/L)	CHOL (mmol/L)	TP (g/L)	ALB (g/L)	GLOB (g/L)
2408	-13	11.8	60	0.33	3.52	73.2	44.8	28.4
	-6	7.8	56	0.39	3.97	73.8	43.7	30.1
	2	7.6	59	0.31	3.72	72.5	44.6	27.9
	7	7.2	59	0.18	4.03	72.1	45.9	26.2
	14	7.3	59	0.21	4.50	69.8	44.5	25.3
	42	9.0	65	0.49	4.78	70.9	44.2	26.7
AB001 100 mg/kg	Day(s) Relative toStart Date	UREA (mmol/L)	CREA (μmol/L)	TG (mmol/L)	CHOL (mmol/L)	TP (g/L)	ALB (g/L)	GLOB (g/L)
2510	-13	9.8	73	0.63	2.42	78.2	40.7	37.5
	-6	7.7	66	0.64	2.36	73.1	38.9	34.2
	2	6.6	64	0.62	2.25	74.0	38.8	35.2
	7	7.9	81	0.70	2.67	73.7	41.8	31.9
	14	8.2	65	0.49	2.68	70.6	42.4	28.2
	42	7.3	72	0.64	2.35	66.7	40.4	26.3

Abbreviations:

UREA	Urea
CREA	Creatinine
TG	Triglycerides
CHOL	Total Cholestrol
TP	Total Protein
ALB	Albumin
GLOB	Globulin

FIGURE 19

Female Chemistry III

Vehicle Control	Day(s) Relative to Start Date	A/G	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	IgA (g/L)	IgG (g/L)	IgM (g/L)
2102	-13	1.4	153	4.10	109.4	0.89	9.86	0.62
	-6	1.4	152	4.52	106.6	0.96	8.70	0.68
	2	1.4	148	3.61	108.6	0.84	7.70	0.57
	7	1.5	148	3.72	108.6	0.92	7.93	0.58
	14	1.4	148	3.40	107.5	1.00	8.28	0.66
	42	1.5	145	3.41	105.2	1.02	9.33	0.67

AB001 0.1 mg/kg	Day(s) Relative toStart Date	A/G	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	IgA (g/L)	IgG (g/L)	IgM (g/L)
2204	-13	1.1	155	4.49	114.2	1.96	11.39	1.60
	-6	1.2	150	4.64	107.6	1.98	10.79	1.81
	2	1.1	147	3.94	109.5	1.65	9.50	1.40
	7	1.2	150	4.10	110.7	1.68	10.24	1.46
	14	1.1	150	4.27	110.4	1.72	10.01	1.53
	42	1.3	145	3.52	104.5	2.06	12.23	1.85

AB001 1 mg/kg	Day(s) Relative toStart Date	A/G	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	IgA (g/L)	IgG (g/L)	IgM (g/L)
2306	-13	1.2	151	4.25	110.9	1.39	9.85	1.59
	-6	1.2	146	4.25	104.7	1.33	9.22	1.49
	2	1.3	145	4.10	107.7	1.25	8.86	1.34
	7	1.5	146	3.71	106.5	1.07	8.53	1.13
	14	1.5	146	4.17	105.2	0.87	8.30	0.90
	42	1.4	144	3.46	103.8	1.05	9.95	0.99

FIGURE 19 - continued

AB001 10 mg/kg	Day(s) Relative toStart Date	A/G	Na (mmol /L)	K (mmol /L)	Cl (mmol /L)	IgA (g/L)	IgG (g/L)	IgM (g/L)
2408	-13	1.6	152	3.36	111.7	0.87	9.36	0.91
	-6	1.5	150	4.26	105.1	0.90	9.12	0.96
	2	1.6	145	3.54	103.1	0.82	9.01	0.87
	7	1.8	145	3.34	105.3	0.63	8.01	0.65
	14	1.8	146	3.62	104.5	0.45	7.15	0.55
	42	1.7	144	3.28	102.2	0.35	9.04	0.47

AB001 100 mg/kg	Day(s) Relative toStart Date	A/G	Na (mmol /L)	K (mmol /L)	Cl (mmol /L)	IgA (g/L)	IgG (g/L)	IgM (g/L)
2510	-13	1.1	152	3.68	112.5	0.96	12.59	0.95
	-6	1.1	148	3.63	107.0	0.98	12.24	0.93
	2	1.1	146	3.77	107.3	0.95	13.16	0.86
	7	1.3	146	3.92	110.2	0.72	10.76	0.74
	14	1.5	147	3.64	109.0	0.47	9.24	0.54
	42	1.5	145	3.23	107.3	0.13	7.71	0.24

Abbreviations:

A/G	Albumin/Globulin Ratio
Na	Sodium
K	Potassium Chloride
Cl	Chloride
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M

FIGURE 20

Male Cytokine Profile I

Vehicle Control	Day(s) Relative toStart Date	IL-2 (pg/mL)	IL-4 (pg/mL)	IL-6 (pg/mL)	IL-10 (pg/mL)	IFN-γ (pg/mL)
1101	1 (PrD0M)	0.000	0.000	0.000	0.000	0.000
	1 (1HPD)	0.000	0.000	61.490	0.000	0.000
	1 (3HPD)	0.000	0.000	13.070	0.000	0.000
	1 (8HPD)	0.000	2.000	10.280	0.000	0.000
	2	0.000	0.420	0.000	0.000	0.000
	3	0.000	0.000	0.000	0.000	0.000
	7	0.000	0.000	0.000	0.000	0.000

AB001 0.1 mg/kg	Day(s) Relative toStart Date	IL-2 (pg/mL)	IL-4 (pg/mL)	IL-6 (pg/mL)	IL-10 (pg/mL)	IFN-γ (pg/mL)
1203	1 (PrD0M)	0.000	0.000	0.000	0.000	0.000
	1 (1HPD)	0.000	0.000	22.110	0.000	0.000
	1 (3HPD)	0.000	0.000	16.130	0.000	0.000
	1 (8HPD)	0.000	0.000	19.480	0.000	0.000
	2	0.000	0.000	1.990	0.000	0.000
	3	0.000	0.000	0.000	0.000	0.000
	7	0.000	0.000	0.000	0.000	0.000

AB001 1 mg/kg	Day(s) Relative toStart Date	IL-2 (pg/mL)	IL-4 (pg/mL)	IL-6 (pg/mL)	IL-10 (pg/mL)	IFN-γ (pg/mL)
1305	1 (PrD0M)	0.000	0.000	0.000	0.000	0.000
	1 (1HPD)	0.000	0.000	88.650	1.780	0.000
	1 (3HPD)	0.000	0.000	28.720	0.000	0.000
	1 (8HPD)	0.000	0.000	6.200	0.000	0.000
	2	0.000	0.000	0.000	0.000	0.000
	3	0.000	0.000	0.420	0.000	0.000
	7	0.000	0.000	0.000	0.000	0.000

FIGURE 20 - continued

AB001 10 mg/kg	Day(s) Relative toStart Date	IL-2 (pg/mL)	IL-4 (pg/mL)	IL-6 (pg/mL)	IL-10 (pg/mL)	IFN-γ (pg/mL)
1407	1 (PrD0M)	0.000	0.000	0.000	0.000	0.000
	1 (1HPD)	0.000	0.000	23.140	0.000	0.000
	1 (3HPD)	0.000	0.000	14.430	0.000	0.000
	1 (8HPD)	0.000	0.000	0.000	0.000	0.000
	2	0.000	0.000	0.000	0.000	0.000
	3	0.000	0.000	0.000	0.000	0.000
	7	0.000	0.000	0.000	0.000	0.000

AB001 100 mg/kg	Day(s) Relative toStart Date	IL-2 (pg/mL)	IL-4 (pg/mL)	IL-6 (pg/mL)	IL-10 (pg/mL)	IFN-γ (pg/mL)
1509	1 (PrD0M)	0.000	0.000	0.000	0.000	0.000
	1 (1HPD)	0.000	3.240	108.130	86.190	10.180
	1 (3HPD)	0.000	3.060	103.970	0.000	13.000
	1 (8HPD)	0.000	0.870	52.660	25.630	8.950
	2	0.000	0.000	30.330	0.000	6.820
	3	0.000	0.000	3.150	20.440	0.000
	7	0.000	0.000	0.000	0.000	0.000

Abbreviation	Description
nPrD0M	Pre Dose 0 min
1HPD	1 Hr Post Dose
3HPD	3 Hr Post Dose
8HPD	8 Hr Post Dose

FIGURE 21

Male Cytokine Panel II

Vehicle Control	Day(s) Relative toStart Date	TNF-α (pg/mL)	IL-17A (pg/mL)	IL-5 (pg/mL)	IL-13 (pg/mL)	IL-21 (pg/mL)
1101	1 (PrD0M)	0.000	0.000	0.00	0.00	0.00
	1 (1HPD)	0.000	0.000	0.00	0.00	0.00
	1 (3HPD)	0.000	0.000	0.00	0.00	0.00
	1 (8HPD)	0.000	0.000	0.00	0.00	0.00
	2	0.000	0.000	0.00	0.00	0.00
	3	0.000	0.000	0.00	0.00	0.00
	7	0.000	0.000	0.00	0.00	0.00

AB001 0.1 mg/kg	Day(s) Relative toStart Date	TNF-α (pg/mL)	IL-17A (pg/mL)	IL-5 (pg/mL)	IL-13 (pg/mL)	IL-21 (pg/mL)
1203	1 (PrD0M)	0.000	0.000	0.00	0.00	0.00
	1 (1HPD)	0.000	0.000	0.00	0.00	0.00
	1 (3HPD)	0.000	0.000	0.00	0.00	0.00
	1 (8HPD)	0.000	0.000	0.00	0.00	0.00
	2	0.000	0.000	0.00	0.00	0.00
	3	0.000	0.000	0.00	0.00	0.00
	7	0.000	0.000	0.00	0.00	0.00

AB001 1 mg/kg	Day(s) Relative toStart Date	TNF-α (pg/mL)	IL-17A (pg/mL)	IL-5 (pg/mL)	IL-13 (pg/mL)	IL-21 (pg/mL)
1305	1 (PrD0M)	0.000	0.000	0.00	0.00	0.00
	1 (1HPD)	0.000	0.000	0.00	0.00	0.00
	1 (3HPD)	0.000	0.000	0.00	0.00	0.00
	1 (8HPD)	0.000	0.000	0.00	0.00	0.00
	2	0.000	0.000	0.00	0.00	0.00
	3	0.000	0.000	0.00	0.00	0.00
	7	0.000	0.000	0.00	0.00	0.00

FIGURE 21- continued

AB001 10 mg/kg	Day(s) Relative toStart Date	TNF-α (pg/mL)	IL-17A (pg/mL)	IL-5 (pg/mL)	IL-13 (pg/mL)	IL-21 (pg/mL)
1407	1 (PrD0M)	0.000	0.000	0.00	0.00	0.00
	1 (1HPD)	0.000	0.000	0.00	0.00	0.00
	1 (3HPD)	0.000	0.000	0.00	0.00	0.00
	1 (8HPD)	0.000	0.000	0.00	0.00	0.00
	2	0.000	0.000	0.00	0.00	0.00
	3	0.000	0.000	0.00	0.00	0.00
	7	0.000	0.000	0.00	0.00	0.00

AB001 100 mg/kg	Day(s) Relative toStart Date	TNF-α (pg/mL)	IL-17A (pg/mL)	IL-5 (pg/mL)	IL-13 (pg/mL)	IL-21 (pg/mL)
1509	1 (PrD0M)	0.000	0.000	0.00	0.00	0.00
	1 (1HPD)	0.000	6.660	0.00	0.00	0.00
	1 (3HPD)	0.000	3.330	0.00	0.00	0.00
	1 (8HPD)	0.000	5.190	0.00	0.00	0.00
	2	0.000	0.000	0.00	0.00	0.00
	3	0.000	0.000	0.00	0.00	0.00
	7	0.000	0.000	0.00	0.00	0.00

Abbreviation	Description
nPrD0M	Pre Dose 0 min
1HPD	1 Hr Post Dose
3HPD	3 Hr Post Dose
8HPD	8 Hr Post Dose

FIGURE 22

Female Cytokine Panel I

Vehicle Control	Day(s) Relative toStart Date	IL-2 (pg/mL)	IL-4 (pg/mL)	IL-6 (pg/mL)	IL-10 (pg/mL)	IFN-γ (pg/mL)
2102	1 (PrD0M)	0.000	0.420	0.000	0.000	0.000
	1 (1HPD)	0.000	3.240	46.950	7.560	0.000
	1 (3HPD)	0.000	4.820	34.150	7.560	8.110
	1 (8HPD)	0.000	5.030	17.610	1.780	8.110
	2	0.000	0.720	0.000	0.000	0.000
	3	0.000	0.000	10.520	0.000	0.000
	7	0.000	1.340	0.000	20.440	0.000

AB001 0.1 mg/kg	Day(s) Relative toStart Date	IL-2 (pg/mL)	IL-4 (pg/mL)	IL-6 (pg/mL)	IL-10 (pg/mL)	IFN-γ (pg/mL)
2204	1 (PrD0M)	0.000	0.000	0.000	0.000	0.000
	1 (1HPD)	0.000	0.000	64.900	18.750	0.000
	1 (3HPD)	0.000	0.000	27.940	0.000	0.000
	1 (8HPD)	0.000	2.170	8.170	0.000	0.000
	2	0.000	2.340	0.000	0.000	0.000
	3	0.000	0.720	0.000	10.630	0.000
	7	0.000	0.000	0.000	0.000	0.000

AB001 1 mg/kg	Day(s) Relative toStart Date	IL-2 (pg/mL)	IL-4 (pg/mL)	IL-6 (pg/mL)	IL-10 (pg/mL)	IFN-γ (pg/mL)
2306	1 (PrD0M)	0.000	2.170	0.000	0.000	5.460
	1 (1HPD)	0.000	0.000	55.080	1.780	0.000
	1 (3HPD)	0.000	0.000	29.120	0.000	0.000
	1 (8HPD)	0.000	0.870	15.270	0.000	4.460
	2	0.000	0.280	0.000	0.000	3.350
	3	0.000	0.000	0.000	0.000	0.000
	7	0.000	2.520	0.000	0.000	8.530

FIGURE 22- continued

AB001 10 mg/kg	Day(s) Relative toStart Date	IL-2 (pg/mL)	IL-4 (pg/mL)	IL-6 (pg/mL)	IL-10 (pg/mL)	IFN-γ (pg/mL)
2408	1 (PrD0M)	0.000	0.000	0.000	0.000	0.000
	1 (1HPD)	0.000	0.000	13.070	0.000	0.000
	1 (3HPD)	0.000	0.000	0.000	0.000	0.000
	1 (8HPD)	0.000	0.000	0.000	0.000	0.000
	2	0.000	0.000	0.000	0.000	0.000
	3	0.000	2.170	0.000	0.000	0.000
	7	0.000	0.000	0.000	0.000	0.000

AB001 100 mg/kg	Day(s) Relative toStart Date	IL-2 (pg/mL)	IL-4 (pg/mL)	IL-6 (pg/mL)	IL-10 (pg/mL)	IFN-γ (pg/mL)
2510	1 (PrD0M)	0.000	0.000	0.000	0.000	0.000
	1 (1HPD)	0.000	1.180	32.840	0.000	0.000
	1 (3HPD)	0.000	2.170	7.280	0.000	8.110
	1 (8HPD)	0.000	0.000	0.000	0.000	0.000
	2	0.000	0.000	0.000	0.000	0.000
	3	0.000	0.000	0.000	0.000	0.000
	7	0.000	2.170	0.000	4.610	10.180

Abbreviation	Description
nPrD0M	Pre Dose 0 min
1HPD	1 Hr Post Dose
3HPD	3 Hr Post Dose
8HPD	8 Hr Post Dose

FIGURE 23

Female Cytokine Panel I

Vehicle Control	Day(s) Relative toStart Date	TNF-α (pg/mL)	IL-17A (pg/mL)	IL-5 (pg/mL)	IL-13 (pg/mL)	IL-21 (pg/mL)
2102	1 (PrD0M)	0.000	0.000	0.00	0.00	0.00
	1 (1HPD)	0.000	5.960	0.00	0.00	0.00
	1 (3HPD)	0.000	10.280	0.00	0.00	0.00
	1 (8HPD)	0.000	9.720	0.00	0.00	0.00
	2	0.000	0.000	0.00	0.00	0.00
	3	0.000	0.000	0.00	0.00	0.00
	7	0.000	13.950	0.00	0.00	0.00

AB001 0.1 mg/kg	Day(s) Relative toStart Date	TNF-α (pg/mL)	IL-17A (pg/mL)	IL-5 (pg/mL)	IL-13 (pg/mL)	IL-21 (pg/mL)
2204	1 (PrD0M)	0.000	0.000	0.00	0.00	0.00
	1 (1HPD)	0.000	5.190	0.00	0.00	0.00
	1 (3HPD)	0.000	0.000	0.00	0.00	0.00
	1 (8HPD)	0.000	0.000	0.00	0.00	0.00
	2	0.000	0.000	0.00	0.00	0.00
	3	0.000	4.340	0.00	0.00	0.00
	7	0.000	0.000	0.00	0.00	0.00

AB001 1 mg/kg	Day(s) Relative toStart Date	TNF-α (pg/mL)	IL-17A (pg/mL)	IL-5 (pg/mL)	IL-13 (pg/mL)	IL-21 (pg/mL)
2306	1 (PrD0M)	0.000	10.830	0.00	0.00	0.00
	1 (1HPD)	0.000	0.000	0.00	0.00	0.00
	1 (3HPD)	0.000	0.000	0.00	0.00	0.00
	1 (8HPD)	0.000	8.560	0.00	0.00	0.00
	2	0.000	7.330	0.00	0.00	0.00
	3	0.000	0.000	0.00	0.00	0.00
	7	0.000	11.890	0.00	0.00	0.00

FIGURE 23- continued

AB001 10 mg/kg	Day(s) Relative toStart Date	TNF-α (pg/mL)	IL-17A (pg/mL)	IL-5 (pg/mL)	IL-13 (pg/mL)	IL-21 (pg/mL)
2408	1 (PrD0M)	0.000	0.000	0.00	0.00	0.00
	1 (1HPD)	0.000	0.000	0.00	0.00	0.00
	1 (3HPD)	0.000	0.000	0.00	0.00	0.00
	1 (8HPD)	0.000	0.000	0.00	0.00	0.00
	2	0.000	0.000	0.00	0.00	0.00
	3	0.000	0.000	0.00	0.00	0.00
	7	0.000	0.000	0.00	0.00	0.00

AB001 100 mg/kg	Day(s) Relative toStart Date	TNF-α (pg/mL)	IL-17A (pg/mL)	IL-5 (pg/mL)	IL-13 (pg/mL)	IL-21 (pg/mL)
2510	1 (PrD0M)	0.000	0.000	0.00	0.00	0.00
	1 (1HPD)	0.000	5.960	0.00	0.00	0.00
	1 (3HPD)	0.000	13.440	0.00	0.00	0.00
	1 (8HPD)	0.000	0.000	0.00	0.00	0.00
	2	0.000	0.000	0.00	0.00	0.00
	3	0.000	0.000	0.00	0.00	0.00
	7	0.000	11.890	0.00	0.00	0.00

Abbreviation	Description
nPrD0M	Pre Dose 0 min
1HPD	1 Hr Post Dose
3HPD	3 Hr Post Dose
8HPD	8 Hr Post Dose

FIGURE 24

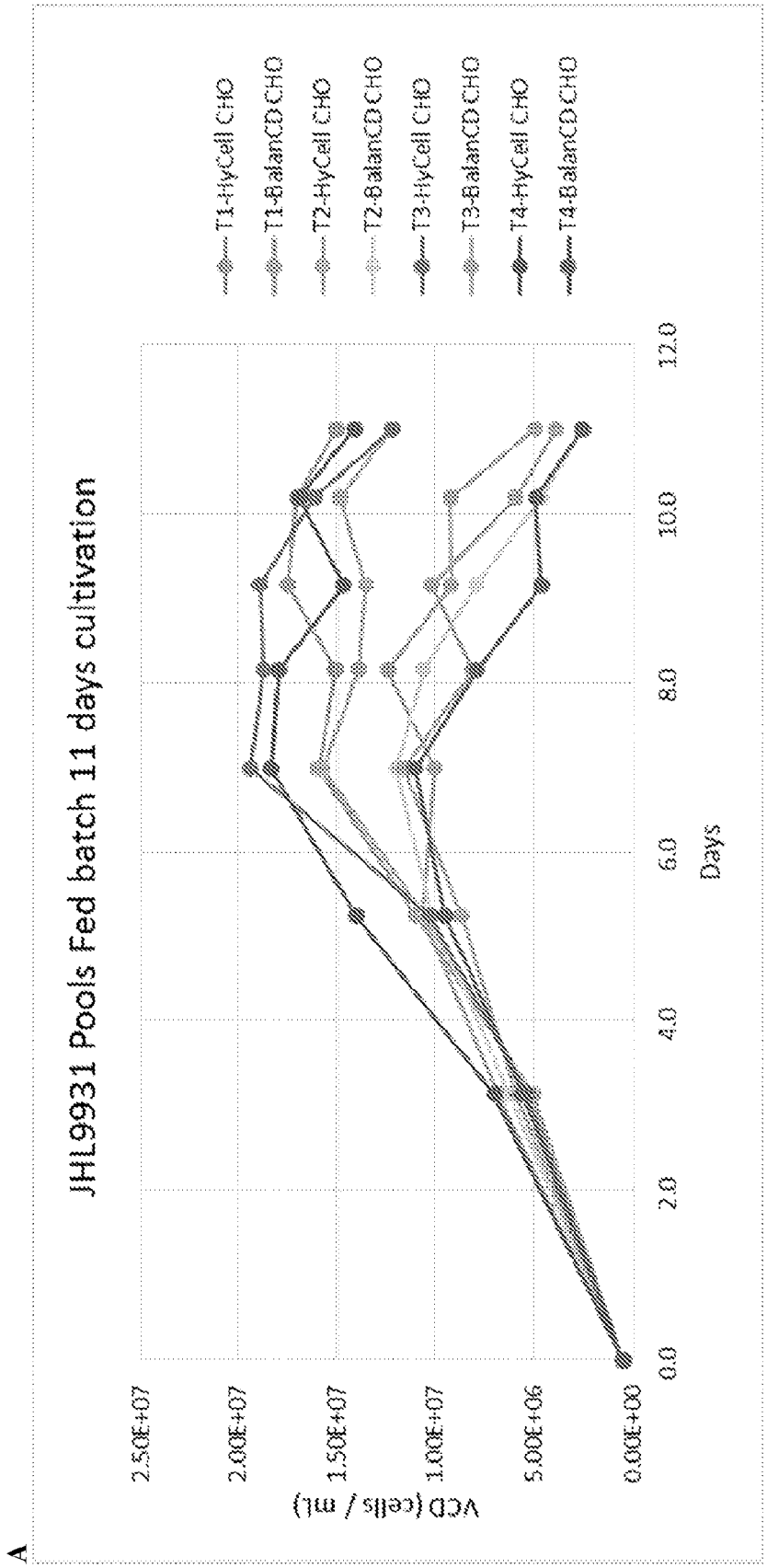

A
JHL9931 Pools Fed batch 11 days cultivation
VCD (cells / mL)
2.50E+07
2.00E+07
1.50E+07
1.00E+07
5.00E+06
0.00E+00
0.0
2.0
4.0
6.0
8.0
10.0
12.0
Days
T1-HyCell CHO
T1-BalanCD CHO
T2-HyCell CHO
T2-BalanCD CHO
T3-HyCell CHO
T3-BalanCD CHO
T4-HyCell CHO
T4-BalanCD CHO

FIGURE 24 - continued

B

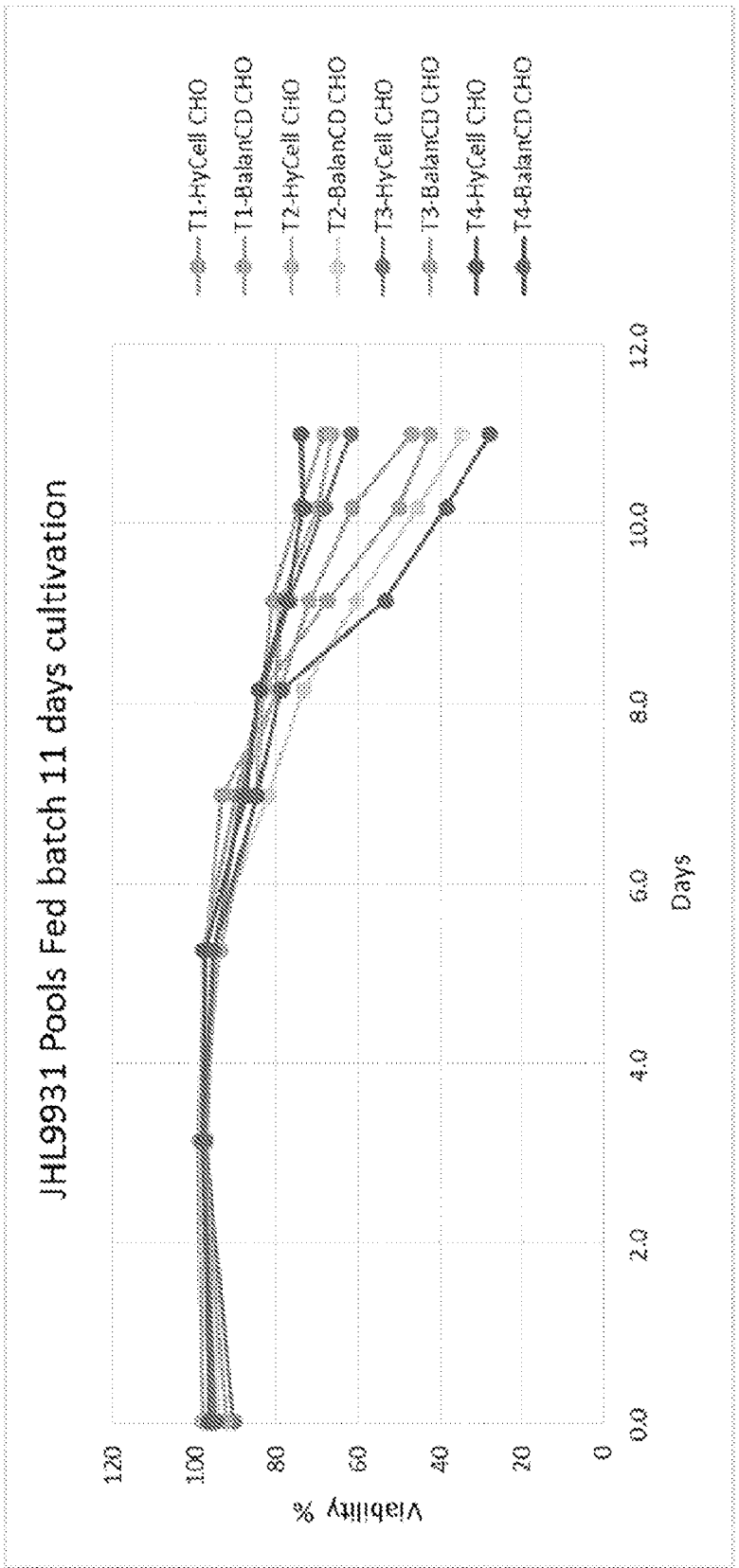


FIGURE 25

A
1 2 3 4 5 6 7 8
(KDa)
150
100
75
50
37
25
Lane 1 : JHL9931_T3_HyCell CHO
Lane 2 : JHL9931_T3_BalanCD CHO
Lane 3 : JHL9931_T4_HyCell CHO
Lane 4 : JHL9931_T4_BalanCD CHO
Lane 5 : JHL9931_T3_HyCell CHO (+ PNGaseF)
Lane 6 : JHL9931_T3_BalanCD CHO(+PNGaseF)
Lane 7 : JHL9931_T4_HyCell CHO(+PNGaseF)
Lane 8 : JHL9931_T4_BalanCD CHO(+PNGaseF)
B
1 2 3 4 5 6 7 8
(KDa)
150
100
75
50
37
25
Lane 1 : JHL9931_T3_HyCell CHO
Lane 2 : JHL9931_T3_BalanCD CHO
Lane 3 : JHL9931_T4_HyCell CHO
Lane 4 : JHL9931_T4_BalanCD CHO
Lane 5 : JHL9931_T3_HyCell CHO (+ PNGaseF)
Lane 6 : JHL9931_T3_BalanCD CHO(+PNGaseF)
Lane 7 : JHL9931_T4_HyCell CHO(+PNGaseF)
Lane 8 : JHL9931_T4_BalanCD CHO(+PNGaseF)

FIGURE 26

Pools	clone ID	IVCD	Day 12 viability	Titer (g/L)	Day 0 image of Monoclonality
T4	2B6	1.54E+08	71.0	2.7	ok
	4C4	1.42E+08	60.5	2.6	ok
	4H8	1.18E+08	73.0	2.6	ok
	3C7	1.27E+08	72.5	2.1	ok
	4A3	1.35E+08	58.0	2.1	ok
	4B10	1.02E+08	66.0	2.1	ok
	3B4	1.07E+08	24.0	1.9	ok
	3F5	8.81E+07	49.5	1.8	ok
	2C7	1.27E+08	68.5	1.8	ok
	1C7	8.10E+07	82.0	1.7	ok
	3E10	9.36E+07	33.5	1.6	ok
	1F6	7.55E+07	72.0	1.6	ok
	4F1	1.28E+08	67.0	1.6	ok
	2F2	1.53E+08	55.5	1.6	ok
	2D8	9.63E+07	64.0	1.5	ok
	1C6	1.31E+08	33.0	1.5	ok
	4E4	1.20E+08	61.5	1.5	ok
	1D2	1.27E+08	62.5	1.4	ok
	4D7	1.14E+08	62.5	1.0	ok
T3	4B10	7.88E+07	54.0	2.5	ok
	2F12	7.65E+07	60.0	2.3	ok
	2H7	1.06E+08	66.5	2.3	ok
	2D3	1.09E+08	58.5	2.1	ok
	4D2	1.17E+08	59.5	2.1	ok
	1D3	6.12E+07	66.0	2.0	ok
	3G4	7.83E+07	63.5	2.0	ok
	3H9	9.84E+07	54.0	1.9	ok
	1G5	1.18E+08	70.5	1.9	ok
	2H3	8.87E+07	62.5	1.8	ok
	3D3	7.63E+07	61.5	1.8	ok
	2G3	9.55E+07	82.0	1.7	ok
	2F3	6.78E+07	59.0	1.7	ok
	3E9	1.07E+08	64.0	1.6	ok
	1F8	6.75E+07	68.0	1.2	ok
	1D11	9.41E+07	46.0	0.8	ok

FIGURE 27

Clone name	T4-2B6	T4-4H8	T4-3C7	T4-1C7	T4-1F6	T3-2H7	T3-1F8	T3-1G5	T3-1D3	T3-2G3
High Mannose	5.1	5.5	5.9	4.2	5	4.1	4.8	4.8	6.4	5.1
Sialylation	36	37.7	34.7	38.9	38.5	17	15.8	17.5	22.7	22.3
Galactosylation	35.2	35.4	35.1	32.5	32.4	51	32.3	50.2	45.7	47.5
Afucosylation	5.9	5.4	5.4	4.1	4.7	5.9	4.2	6	4.8	5.7
G0-N	0.5	0.4	0.5	0.3	0.4	0.4	0.5	0.4	0.3	0.4
G0F-N	1.1	1.1	1.2	1	1.1	0.8	2.3	1.2	1	1.1
G0	1.8	1.4	1.3	1	1.3	1.8	1.3	1.6	0.9	1.2
G0F	17.9	16.4	16.7	19	18.1	23.9	40.6	23.6	20.7	20.8
Man5	2.9	3	3.7	2.3	2.8	3.2	3.7	3.2	4.3	3.2
G1	2	2.4	2.2	1.6	2	2	1.3	2.6	2.3	3
G1'	0.4	0.3	0.3	0.2	0.3	0.5	0.2	0.4	0.3	0.4
G1F	17.2	17.5	17	16.4	15.7	26.9	16.5	26	24.1	24.3
G1F'	5.9	5.9	5.7	5.8	5.7	9.1	7.1	8.9	7.8	8.3
Man6	1.2	1.4	1.3	1.1	1.2	0.9	0.9	1.2	1.3	1.5
G1S1	1.2	0.9	1.1	1	0.7	1.2	0.9	1	1	0.7
G2F	9.7	9.3	9.9	8.5	8.7	12.5	7.2	12.3	11.2	11.5
Man7-1	0.5	0.4	0.4	0.3	0.4	ND	ND	ND	0.3	ND
Man7-2	0.5	0.7	0.5	0.5	0.6	ND	0.2	0.4	0.5	0.4
G2FS1	14.6	14	13.3	14.1	13.3	7.4	6.1	7.5	9	8.1
G2FS2	13	16.4	12.7	15.2	16	5.4	5.1	6.1	8.7	9.5
G3FS1	3	2.5	2.8	3.5	3.7	1.5	2	1.3	2.1	2.1
G3FS2	2.4	2.2	2.6	2.7	2.5	0.9	1.1	1	1.2	1.1
G3FS3	1.8	1.7	2.2	2.4	2.3	0.6	0.6	0.6	0.7	0.8

FIGURE 28A

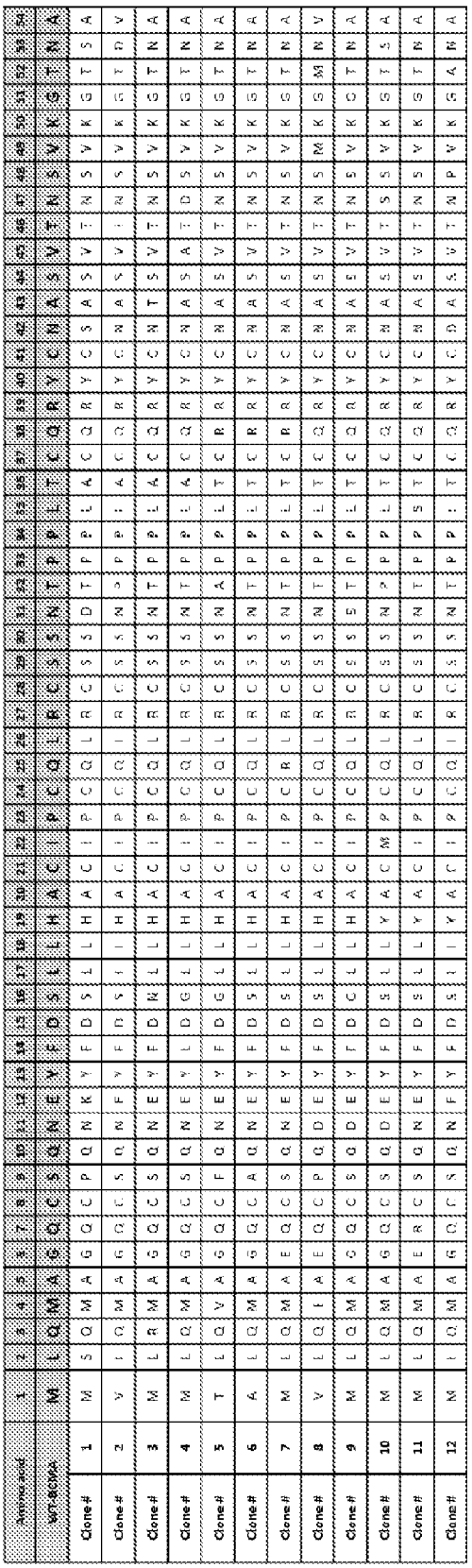


FIGURE 28B

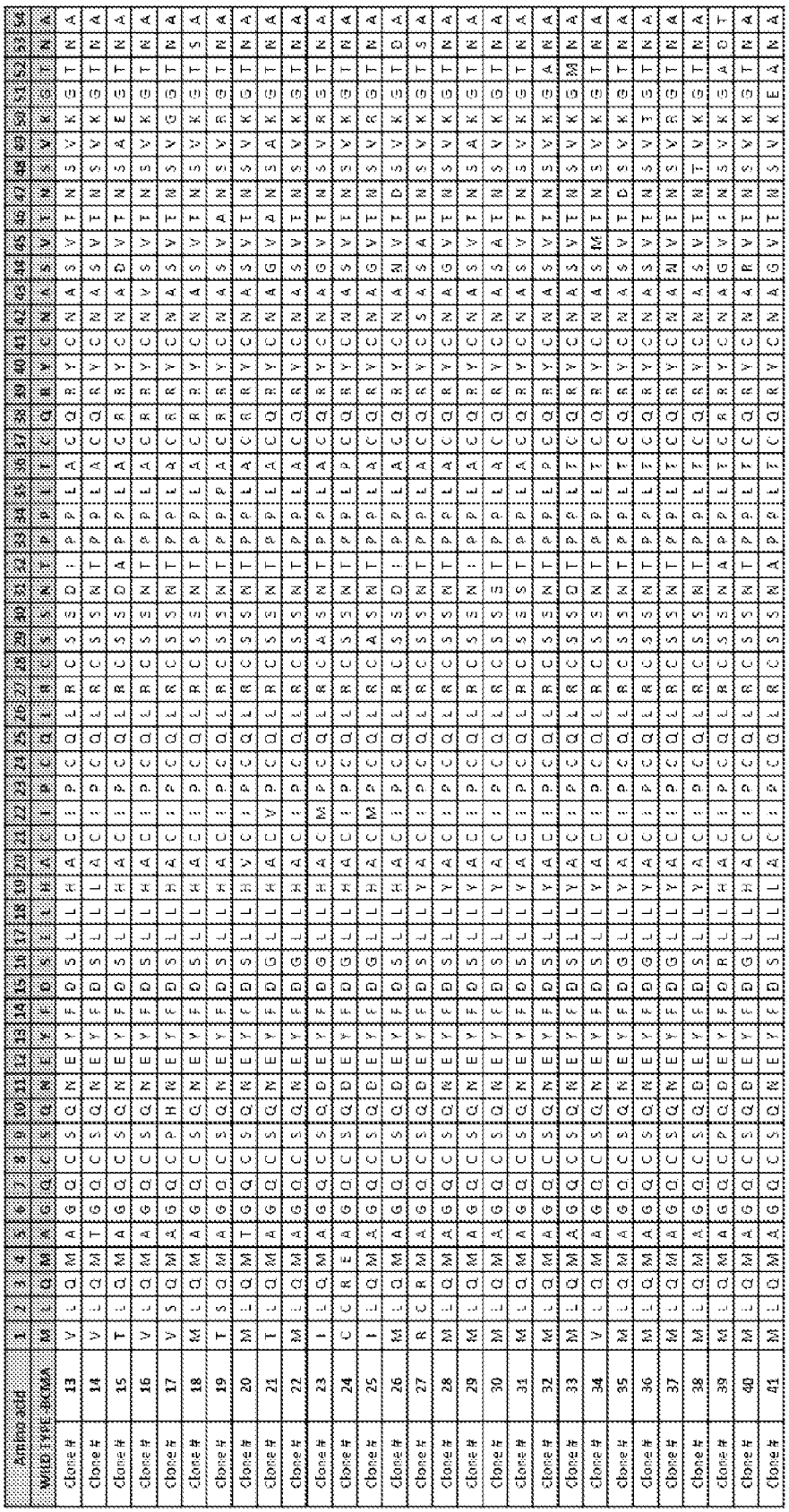


FIGURE 28C

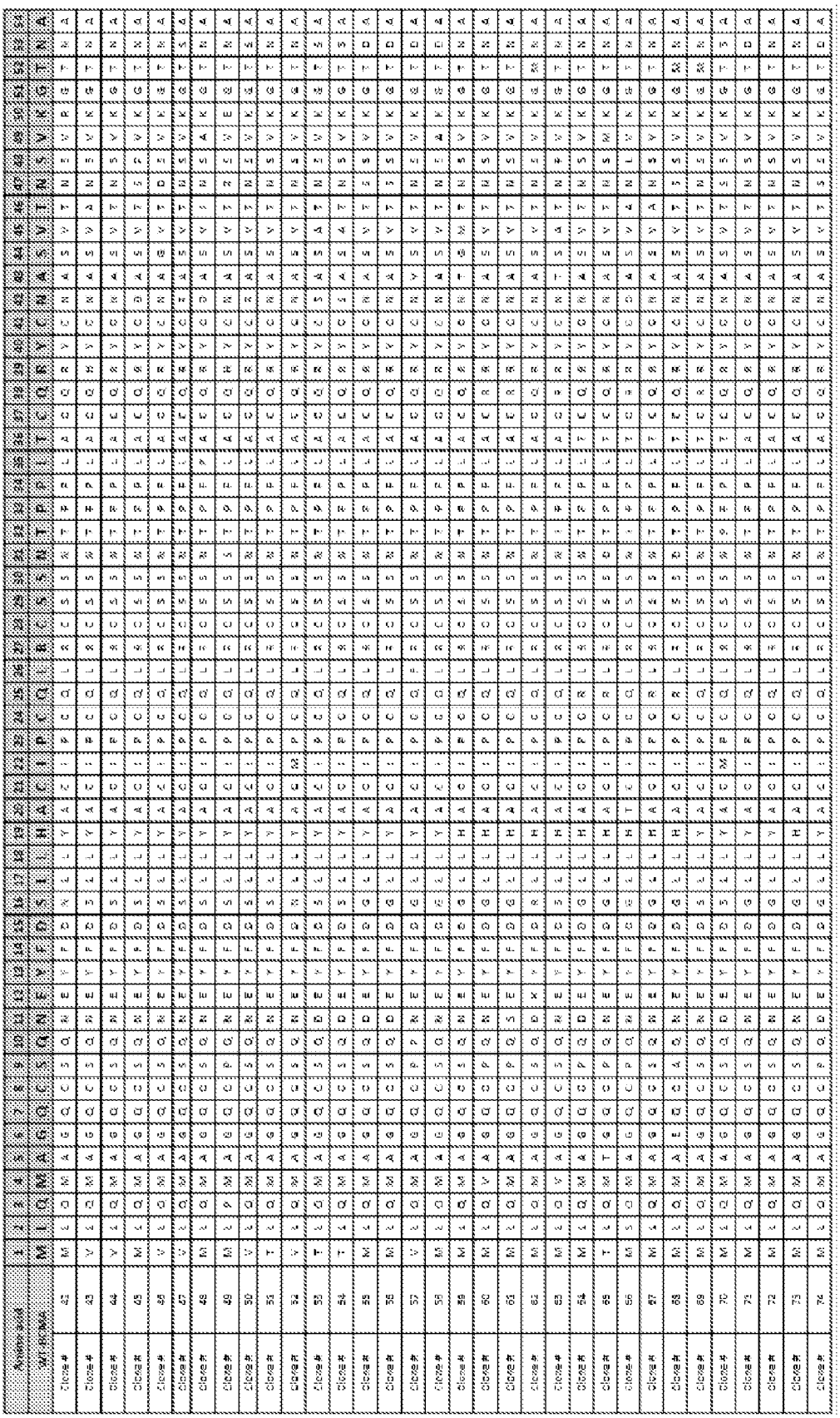


FIGURE 28D

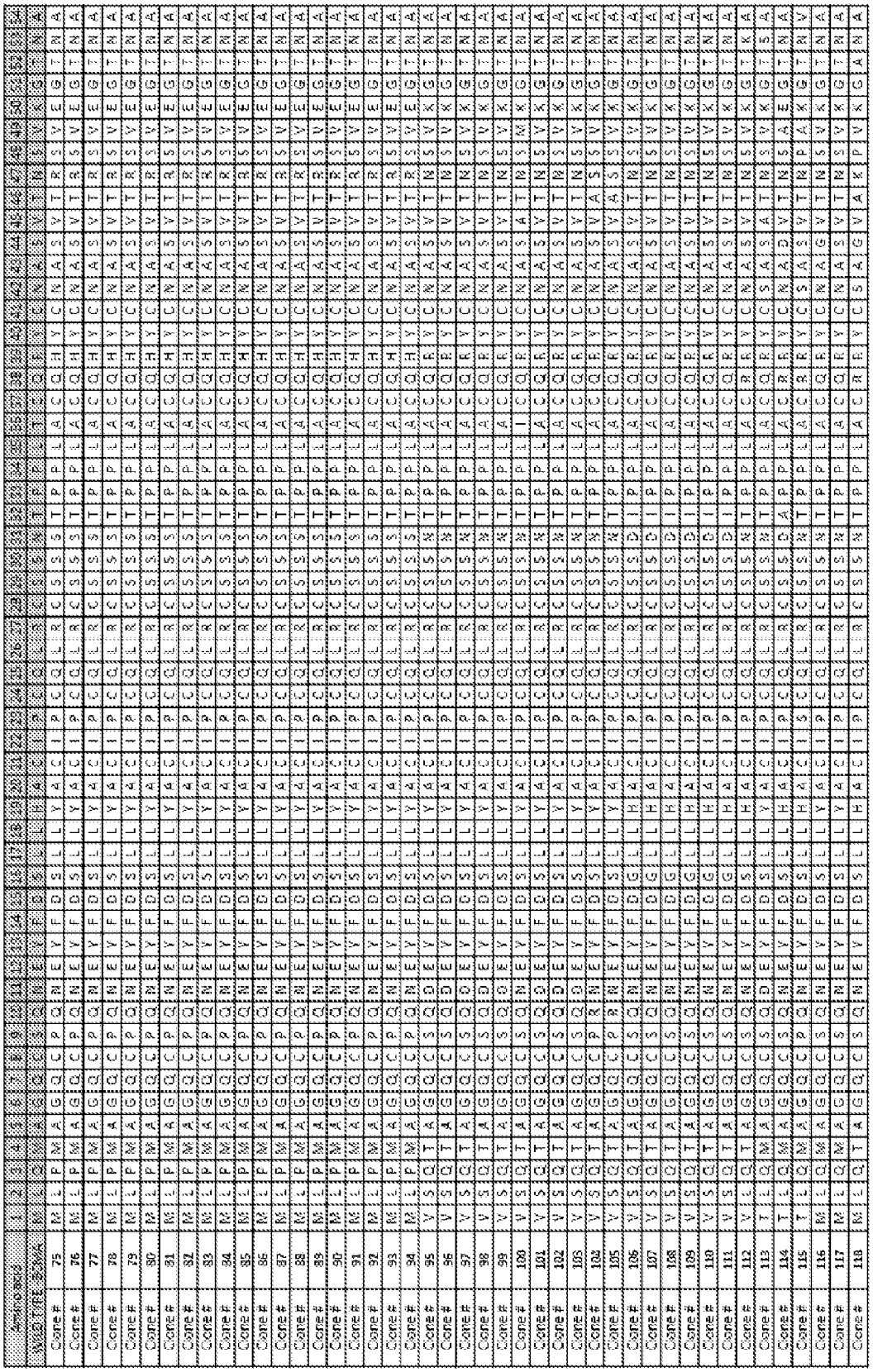


FIGURE 29

SEQ ID NO:80 (Clone #71 + **Linker** + *human IgG1*)
MLQMAGQCSQNEYFDGLLYACIPCQLRCSSNTPPLACQRYCNASVTNSVKGTDA**GGGGS***PKSCDKTHTCPPCPAPELLGG*
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK
LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:81 (Clone #72 + **Linker** + *human IgG1*)
MLQMAGQCSQNEYFDGLLYACIPCQLRCSSNTPPLACQRYCNASVTNSVKGTNA**GGGGS***PKSCDKTHTCPPCPAPELLGG*
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK
LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:82 (Clone #74 + **Linker** + *human IgG1*)
MLQMAGQCPQDEYFDGLLYACIPCQLRCSSNTPPLACQRYCNASVTSSVKGTDA**GGGGS***PKSCDKTHTCPPCPAPELLGG*
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK
LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:83 (Clone #75 + **Linker** + *human IgG1*)
MLPMAGQCPQNEYFDSLLYACIPCQLRCSSSTPPLACQHYCNASVTRSVEGTNA**GGGGS***PKSCDKTHTCPPCPAPELLGGP*
SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL
TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:84 (Clone #106 + **Linker** + *human IgG1*)
VSQTAGQCSQNEYFDGLLHACIPCQLRCSSDIPPLACQRYCNASVTNSVKGTNA**GGGGS***PKSCDKTHTCPPCPAPELLGGP*
SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL
TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

FIGURE 30

SEQ ID NO:1 (Extracellular domain of wild type human BCMA)
MLQMAGQCSQNEYFDSLLHACIPCQLRCSSNTPPLTCQRYCNASVTNSVKGTNA

SEQ ID NO:85 (Extracellular domain of BAFF):
AVQGPEETVTQDCLQLIADSETPTIQKGSYTFVPWLLSFKRGSALEEKENKILVKETGYFFIYGQVLYTDKTYAMGHLI
QRKKVHVFGDELSLVTLFRCIQNMPETLPNNSCYSAGIAKLEEGDELQLAIPRENAQISLDGDVTFFGALKLL

SEQ ID NO:86 (Extracellular domain of APRIL):
AVLTQKQKKQHSVLHLVPINATSKDDSDVTEVMWQPALRRGRGLQAQGYGVRIQDAGVYLLYSQVLFQDVTFTMG
QVVSREGQGRQETLFRCIRSMPSHPDRAYNSCYSAGVFHLHQGDILSVIIPRARAKLNLSPHGTFLGFVKL

SEQ ID NO:87 (a linker domain)
IEGRMD

SEQ ID NO:88 (a linker domain)
GGGGS

FIGURE 31

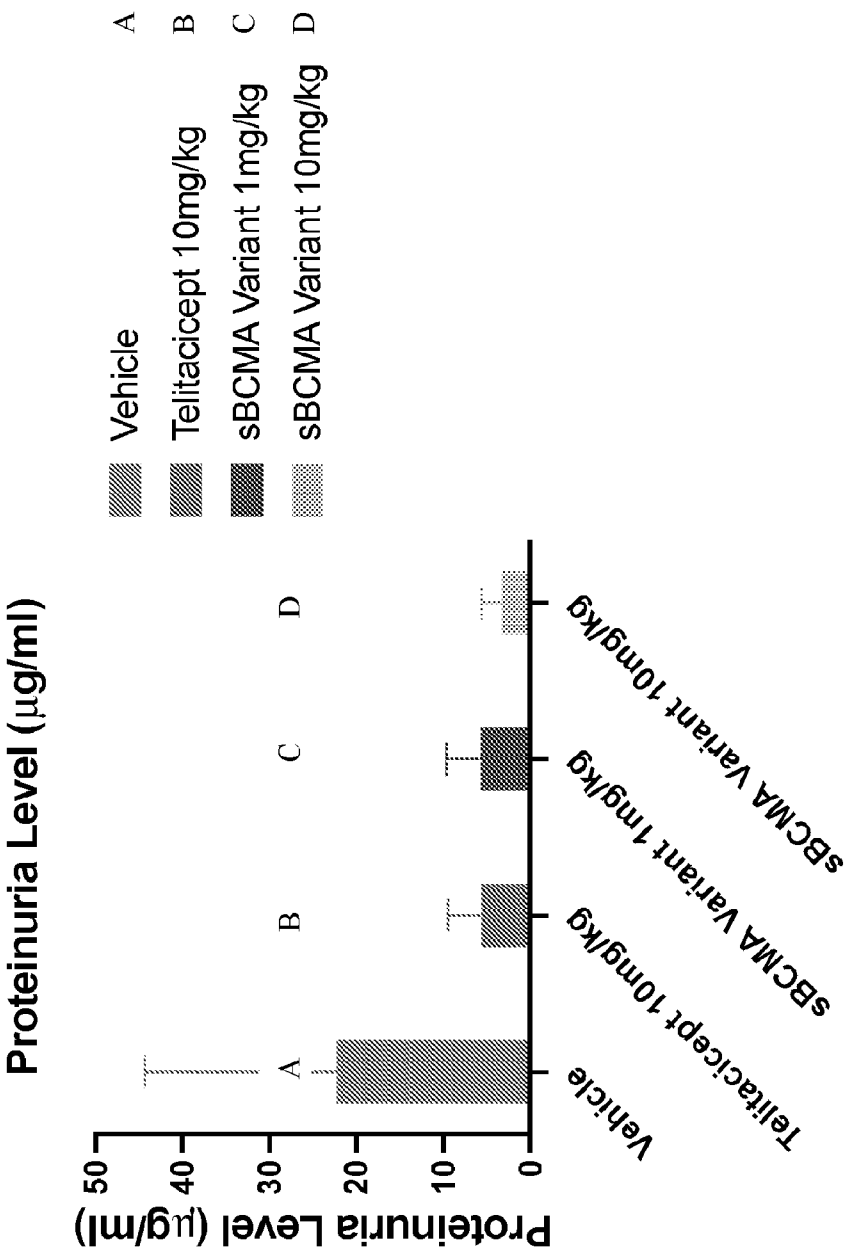
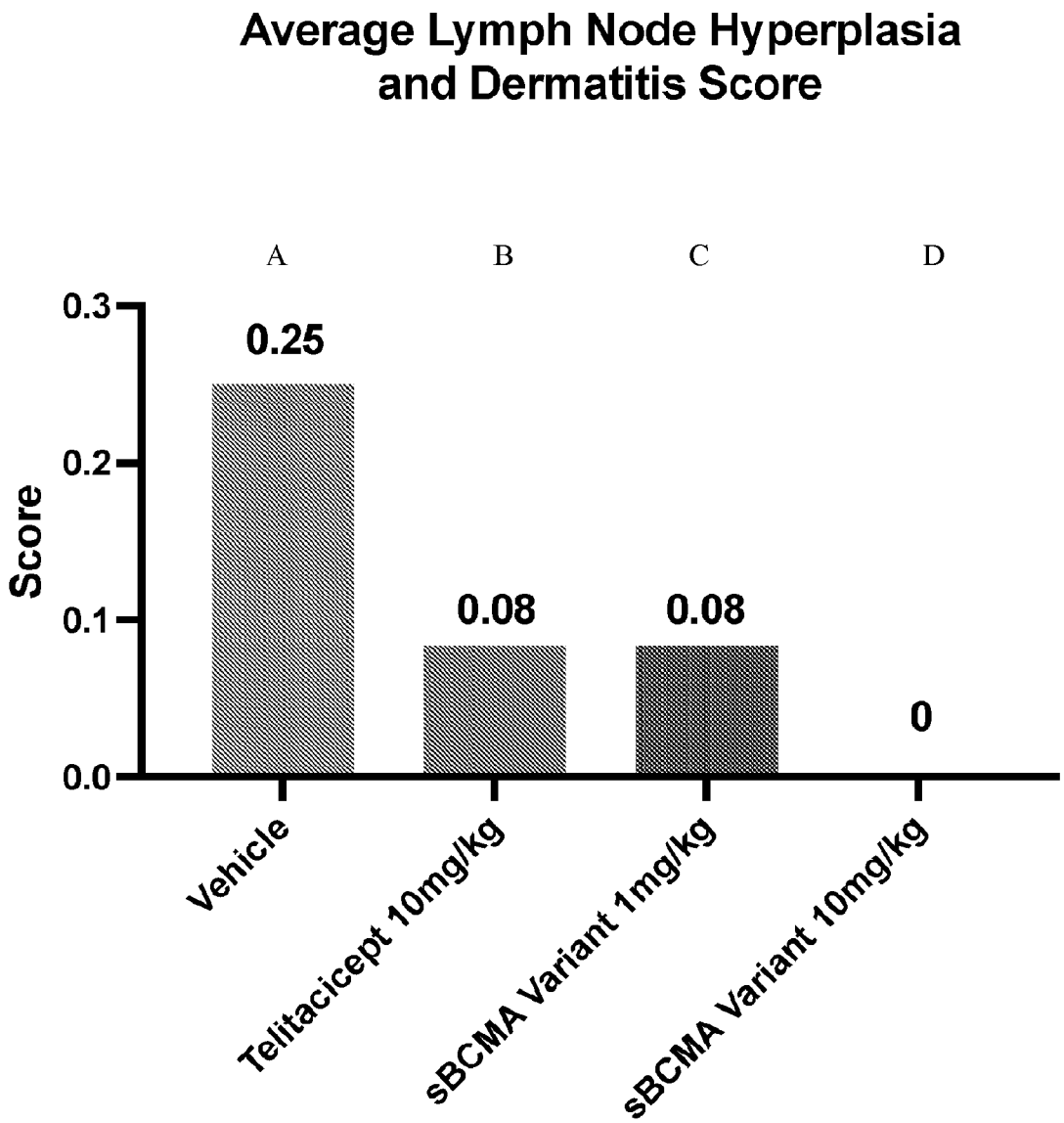

Proteinuria Level (μg/ml)
Vehicle
Telitacicept 10mg/kg
sBCMA Variant 1mg/kg
sBCMA Variant 10mg/kg
A
B
C
D
Proteinuria Level (μg/ml)
0
10
20
30
40
50
Vehicle
Telitacicept 10mg/kg
sBCMA Variant 1mg/kg
sBCMA Variant 10mg/kg

FIGURE 32


Average Lymph Node Hyperplasia and Dermatitis Score
A
B
C
D
0.3
0.2
0.1
0.0
Score
0.25
0.08
0.08
0
Vehicle
Telitacicept 10mg/kg
sBCMA Variant 1mg/kg
sBCMA Variant 10mg/kg