

CLAIMS

WHAT IS CLAIMED:

1. An immunomodulatory protein comprising at least one variant TACI polypeptide, wherein the at least one variant TACI polypeptide comprises one or more amino acid substitutions in the extracellular domain (ECD) of a reference TACI polypeptide at positions selected from among 40, 59, 60, 61, 74, 75, 76, 77, 78, 79, 82, 83, 84, 85, 86, 87, 88, 92, 95, 97, 98, 99, 101, 102 and 103, corresponding to numbering of positions set forth in SEQ ID NO:122.
2. An immunomodulatory protein comprising a variant TACI-Fc fusion protein, the variant TACI-Fc fusion protein comprising a variant TACI polypeptide, an Fc region, and a linker between the TACI polypeptide and Fc region, wherein the variant TACI polypeptide comprises one or more amino acid substitutions in the extracellular domain (ECD) of a reference TACI polypeptide at positions selected from among 40, 59, 60, 61, 74, 75, 76, 77, 78, 79, 82, 83, 84, 85, 86, 87, 88, 92, 95, 97, 98, 99, 101, 102 and 103, corresponding to numbering of positions set forth in SEQ ID NO:122.
3. The immunomodulatory protein of claim 1 or claim 2, wherein the reference TACI polypeptide is a truncated polypeptide consisting of the extracellular domain of TACI or a specific binding portion thereof that binds to APRIL, BAFF, or a BAFF/APRIL heterotrimer.
4. The immunomodulatory protein of any of claims 1-3, wherein the reference TACI polypeptide comprises the sequence of amino acids set forth in SEQ ID NO:122, or a portion thereof comprising one or both of a CRD1 domain and a CRD2 domain that binds to APRIL, BAFF, or a BAFF/APRIL heterotrimer.
5. The immunomodulatory protein of any of claims 1-4, wherein the reference TACI polypeptide lacks an N-terminal methionine.
6. The immunomodulatory protein of any of claims 1-5, wherein the reference TACI polypeptide comprises the CRD1 domain and the CRD2 domain.

7. The immunomodulatory protein of any of claims 1-6, wherein the reference TACI polypeptide comprises the sequence set forth in SEQ ID NO:1.
8. The immunomodulatory protein of any of claims 1-6, wherein the reference TACI polypeptide consists of the sequence set forth in SEQ ID NO:1.
9. The immunomodulatory protein of any of claims 1-5, wherein the reference TACI polypeptide is a truncated wild-type TACI extracellular domain that contains the cysteine rich domain 2 (CRD2) but lacks the entirety of the cysteine rich domain 1 (CRD1), wherein the variant TACI polypeptide comprises one or more amino acid substitutions in the truncated wild-type TACI extracellular domain.
10. The immunomodulatory protein of any of claims 1-5 and 9, wherein the reference TACI polypeptide is a truncated wild-type TACI extracellular domain that consists of a contiguous sequence contained within amino acid residues 67-118 that includes amino acid residues 71-104, with reference to positions set forth in SEQ ID NO:122, wherein the variant TACI polypeptide comprises one or more amino acid substitutions in the truncated wild-type TACI extracellular domain.
11. The immunomodulatory protein of claim 9 or claim 10, wherein the reference TACI polypeptide is a truncated wild-type TACI extracellular domain that is 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 or 51 amino acids in length.
12. The immunomodulatory protein of any of claims 1-5, and 9-11, wherein the reference TACI polypeptide consists essentially of the CRD2 domain.
13. The immunomodulatory protein of any of claims 1-5 and 9-12, wherein the reference TACI polypeptide is a truncated wild-type TACI extracellular domain that consists of amino acid residues 68-110 set forth in SEQ ID NO: 122.
14. The immunomodulatory protein of any of claims 1-5, and 9-13, wherein the reference TACI polypeptide comprises the sequence set forth in SEQ ID NO:13.

15. The immunomodulatory protein of any of claims 1-5, and 9-13, wherein the reference TACI polypeptide consists of the sequence set forth in SEQ ID NO:13.

16. The immunomodulatory protein of any of claims 1-15, wherein the one or more amino acid substitutions are selected from W40R, Q59R, R60G, T61P E74V, Q75E, Q75R, G76S, K77E, F78Y, Y79F, L82H, L82P, L83S, R84G, R84L, R84Q, D85E, D85V, C86Y, I87L, I87M, S88N, I92V, Q95R, P97S, K98T, Q99E, A101D, Y102D, F103S, F103V, F103Y, or a conservative amino acid substitution thereof.

17. The immunomodulatory protein of any of claims 1-16, wherein the one or more amino acid substitutions comprises at least one of E74V, K77E, Y79F, L82H, L82P, R84G, R84L, R84Q, D85V or C86Y.

18. The immunomodulatory protein of any of claims 1-16, wherein the one or more amino acid substitutions comprise an amino acid substitution selected from the group consisting of Q75E, K77E, F78Y, R84G, R84Q, A101D and Y102D, or any combination thereof.

19. The immunomodulatory protein of any of claims 1-16 and 18, wherein the one or more amino acid substitution comprise at least the amino acid substitution Q75E.

20. The immunomodulatory protein of any of claims 1-19, wherein the one or more amino acid substitution comprises at least the amino acid substitution K77E.

21. The immunomodulatory protein of any of claims 1-16 and 18-20, wherein the one or more amino acid substitution comprise at least the amino acid substitution F78Y.

22. The immunomodulatory protein of any of claims 1-17 and 19-21, wherein the one or more amino acid substitution comprises at least the amino acid substitution R84G.

23. The immunomodulatory protein of any of claims 1-21, wherein the one or more amino acid substitution comprises at least the amino acid substitution R84Q.

24. The immunomodulatory protein of any of claims 1-16 and 18-23, wherein the one or more amino acid substitution comprises at least the amino acid substitution A101D.
25. The immunomodulatory protein of any of claims 1-23, wherein the one or more amino acid substitutions comprise Q75E/R84Q, Q75E/K77E, Q75E/F78Y, Q75E/A101D, Q75E/Y102D, F77E/F78Y, K77E/R84Q, K77E/A101D, K77E/Y102D, F78Y/R84Q, F78Y/A101D, F78Y/Y102D, R84Q/A101D, R84Q/Y102D or A101D/Y102D.
26. The immunomodulatory protein of any of claims 1-25, wherein the one or more amino acid substitutions are D85E/K98T, I87L/K98T, R60G/Q75E/L82P, R60G/C86Y, W40R/L82P/F103Y, W40R/Q59R/T61P/K98T, L82P/I87L, G76S/P97S, K77E/R84L/F103Y, Y79F/Q99E, L83S/F103S, K77E/R84Q, K77E/A101D, K77E/F78Y/Y102D, Q75E/R84Q, Q75R/R84G/I92V, K77E/A101D/Y102D, R84Q/S88N/A101D, R84Q/F103V, K77E/Q95R/A101D or I87M/A101D.
27. The immunomodulatory protein of any of claims 1-25, wherein the one or more amino acid substitutions are R84G, A101D, K77E/R84Q, K77E/A101D, K77E/F78Y, K77E/F78Y/Y102D, Q75E/R84Q, K77E/A101D/Y102D, R84Q, K77E, A101D, Q75E, K77E/F78Y/R84Q, F78Y, F78Y/R84Q, F78Y/A101D, F78Y/Y102D, or K77E/Y102D.
28. The immunomodulatory protein of any of claims 1-18, 20, 21, and 25-27, wherein the one or more amino acid substitutions are K77E/F78Y/Y102D.
29. The immunomodulatory protein of any of claims 1-19, 23, and 25-27, wherein the one or more amino acid substitutions are Q75E/R84Q.
30. The immunomodulatory protein of any of claims 1-18, 20 and 24-27, wherein the one or more amino acid substitutions are K77E/A101D/Y102D.

31. The immunomodulatory protein of any of claims 1-30, wherein the variant TACI polypeptide has increased binding affinity to one or both of APRIL and BAFF compared to the reference TACI polypeptide.

32. The immunomodulatory protein of any of claims 1-31, wherein the variant TACI polypeptide has increased binding affinity to APRIL.

33. The immunomodulatory protein of any of claims 1-32, wherein the variant TACI polypeptide has increased binding affinity to BAFF.

34. The immunomodulatory protein of any of claims 1-33, wherein the variant TACI polypeptide has increased binding affinity to APRIL and BAFF.

35. The immunomodulatory protein of any of claims 30-34, wherein the increased binding affinity for BAFF or APRIL is independently increased more than 1.2-fold, 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 20-fold, 30-fold, 40-fold, 50-fold or 60-fold.

36. The immunomodulatory protein of any of claims 30-35, wherein the variant TACI polypeptide has up to 10 amino acid modifications compared to the reference TACI polypeptide.

37. The immunomodulatory protein of an of claims 30-35, wherein the variant TACI polypeptide has up to 5 amino acid modifications compared to the reference TACI polypeptide.

38. The immunomodulatory protein of any of claims 1-37, wherein the variant TACI polypeptide has at least 90% sequence identity to SEQ ID NO:122 or a specific binding fragment thereof comprising the CRD1 domain and/or CRD2 domain.

39. The immunomodulatory protein of any of claims 1-37, wherein the variant TACI polypeptide has at least 95% sequence identity to SEQ ID NO:122 or a specific binding fragment thereof comprising the CRD1 domain and/or CRD2 domain.

40. The immunomodulatory protein of claim 38 or claim 39, wherein the specific binding fragment is set forth in SEQ ID NO:1, SEQ ID NO:13, SEQ ID NO:130 or SEQ ID NO:131.

41. The immunomodulatory protein of any of claims 1-40, wherein the variant TACI polypeptide has at least 90% sequence identity to SEQ ID NO:13.

42. The immunomodulatory protein of any of claims 1-40, wherein the variant TACI polypeptide has at least 95% sequence identity to SEQ ID NO:13.

43. The immunomodulatory protein of any of claims 1-42, wherein:
the variant TACI polypeptide comprises the sequence set forth in any one of SEQ ID NOS: 2-12, 21, 22 and 101-120; or
the variant TACI polypeptide comprises the sequence set forth in any one of SEQ ID NOS: 14-20, 23-35, 92-100 and 177-192.

44. The immunomodulatory protein of any of claims 1-43, wherein:
the variant TACI polypeptide consists or consists essentially of the sequence set forth in any one of SEQ ID NOS: 2-12, 21, 22 and 101-120; or
the variant TACI polypeptide consists or consists essentially of the sequence set forth in any one of SEQ ID NOS: 14-20, 23-35, 92-100 and 177-192.

45. The immunomodulatory protein of any of claims 1-44, wherein the variant TACI polypeptide is set forth in SEQ ID NO: 26.

46. The immunomodulatory protein of any of claims 1-44, wherein the variant TACI polypeptide is set forth in SEQ ID NO:27.

47. An immunomodulatory protein comprising at least one TACI polypeptide that is a truncated wild-type TACI extracellular domain, wherein the truncated wild-type TACI

extracellular domain contains the cysteine rich domain 2 (CRD2) but lacks the entirety of the cysteine rich domain 1 (CRD1).

48. An immunomodulatory protein comprising at least one TACI polypeptide that is a truncated wild-type TACI extracellular domain, wherein the truncated wild-type TACI extracellular domain consists of a contiguous sequence contained within amino acid residues 67-118 that consists of amino acid residues 71-104, with reference to positions set forth in SEQ ID NO:122.

49. An immunomodulatory comprising a TACI-Fc fusion protein, the TACI-Fc fusion protein comprising a truncated wild-type TACI extracellular domain, an Fc region, and a linker between the TACI polypeptide and Fc region, wherein the truncated wild-type TACI extracellular domain contains the cysteine rich domain 2 (CRD2) but lacks the entirety of the cysteine rich domain 1 (CRD1).

50. An immunomodulatory comprising a TACI-Fc fusion protein, the TACI-Fc fusion protein comprising a truncated wild-type TACI extracellular domain, an Fc region, and a linker between the TACI polypeptide and Fc region, wherein the truncated wild-type TACI extracellular domain consists of a contiguous sequence contained within amino acid residues 67-118 that consists of amino acid residues 71-104, with reference to positions set forth in SEQ ID NO:122.

51. The immunomodulatory protein of any of claims 47-50, wherein the truncated wild-type TACI extracellular domain is 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 50, 51 amino acids in length.

52. The immunomodulatory protein of any of claims 47-51, wherein the truncated wild-type TACI extracellular domain consists of amino acid residues 68-110 set forth in SEQ ID NO: 122.

53. The immunomodulatory protein of any of claims 47-51, wherein the truncated wild-type TACI extracellular domain consists of the sequence of amino acid set forth in SEQ ID NO:13.

54. An immunomodulatory protein comprising at least one TACI polypeptide that is a truncated TACI polypeptide consisting of the sequence of amino acid set forth in SEQ ID NO:13.

55. The immunomodulatory protein of any of claims 47-54, wherein the truncated TACI polypeptide binds to APRIL, BAFF, or a BAFF/APRIL heterotrimer.

56. The immunomodulatory protein of any of claims 1, 3-48 and 51-55, comprising a heterologous moiety that is linked to the at least one TACI polypeptide, optionally via a linker.

57. The immunomodulatory protein of claim 56, wherein the heterologous moiety is a half-life extending moiety, a multimerization domain, a targeting moiety that binds to a molecule on the surface of a cell, or a detectable label.

58. The immunomodulatory protein of claim 57, wherein the half-life extending moiety comprises a multimerization domain, albumin, an albumin-binding polypeptide, Pro/Ala/Ser (PAS), a C-terminal peptide (CTP) of the beta subunit of human chorionic gonadotropin, polyethylene glycol (PEG), long unstructured hydrophilic sequences of amino acids (XTEN), hydroxyethyl starch (HES), an albumin-binding small molecule, or a combination thereof.

59. The immunomodulatory protein of any of claims 1, 3-48 and 51-58 that is a TACI-Fc fusion protein, wherein the at least one TACI polypeptide is linked to an Fc region of an immunoglobulin, optionally via a linker.

60. The immunomodulatory protein of any of claims 2, 49, 50, and 56-59, wherein the linker comprises a peptide linker and the peptide linker is selected from GSGGS (SEQ ID NO: 76), GGGGS (G4S; SEQ ID NO: 77), GSGGGGS (SEQ ID NO: 74), GGGSGGGGS

(2xGGGGS; SEQ ID NO: 78), GGGGSGGGGSGGGGS (3xGGGGS; SEQ ID NO: 79), GGGGSGGGGSGGGGSGGGGS (4xGGGGS, SEQ ID NO:84), GGGGSGGGGSGGGGSGGGGSGGGGS (5xGGGGS, SEQ ID NO: 91), GGGGSSA (SEQ ID NO: 80), or GSGGGGSGGGGS (SEQ ID NO:194) or combinations thereof.

61. The immunomodulatory protein of any of claims 2, 49, 50, 59 and 60, wherein the immunoglobulin Fc is an IgG1 Fc domain, or is a variant Fc that exhibits reduced binding affinity to an Fc receptor and/or reduced effector function, optionally as compared to a wild-type IgG1 Fc domain.

62. The immunomodulatory protein of any of claims 2, 49, 50 and 59-61, wherein the immunoglobulin Fc is an IgG1 Fc domain and the Fc comprises the amino acid sequence set forth in SEQ ID NO:81.

63. The immunomodulatory protein of any of claims 2, 49, 50 and 59-61, wherein the immunoglobulin Fc is a variant IgG1 Fc domain comprising one or more amino acid substitutions selected from L234A, L234V, L235A, L235E, G237A, S267K, R292C, N297G, and V302C, by EU numbering.

64. The immunomodulatory protein of claim 63, wherein the immunoglobulin Fc region comprises the amino acid substitutions L234A, L235E and G237A by EU numbering, optionally wherein the Fc region is set forth in any of SEQ ID NOS: 73, 75, 83, 136 or 221.

65. The immunomodulatory protein of claim 63 or claim 64, wherein the immunoglobulin Fc region further comprises the amino acid substitutions A330S and P331S, optionally wherein the Fc region is set forth in SEQ ID NO: 175 or SEQ ID NO:176.

66. The immunomodulatory protein of any one of claims 2, 49, 50, and 59-65, wherein the TACI-Fc fusion protein comprises the structure: TACI polypeptide (TACI)-Linker-Fc region.

67. The immunomodulatory protein of any of claims 2, 49, 50, 59-62 and 66, wherein the TACI-Fc fusion protein is set forth in SEQ ID NO: 168.
68. The immunomodulatory protein of any of claims 2, 49, 50, 59-62 and 66, wherein the TACI-Fc fusion protein is set forth in SEQ ID NO:170.
69. The immunomodulatory protein of any of claims 2, 49, 50, 59-61, and 63-66, wherein the Fc is a variant Fc comprising the amino acid sequence set forth in SEQ ID NO:73.
70. The immunomodulatory protein of any of claims 2, 49, 50, 59-61, 63-66 and 69, wherein the TACI-Fc fusion protein is set forth in SEQ ID NO: 167.
71. The immunomodulatory protein of any of claims 2, 49, 50, 59-61, 63-66 and 69, wherein the TACI-Fc fusion protein is set forth in SEQ ID NO:169.
72. The immunomodulatory protein of any of claims 2, 49, 50, and 59-71 that is a homodimer comprising two identical copies of the TACI-Fc fusion protein.
73. An immunomodulatory protein that is a homodimer comprising two identical copies of the TACI-Fc fusion protein set forth in SEQ ID NO:167 linked by a covalent disulfide bond.
74. An immunomodulatory protein that is a homodimer comprising two identical copies of the TACI-Fc fusion protein set forth in SEQ ID NO:168 linked by a covalent disulfide bond.
75. An immunomodulatory protein that is a homodimer comprising two identical copies of the TACI-Fc fusion protein set forth in SEQ ID NO:169 linked by a covalent disulfide bond.

76. An immunomodulatory protein that is a homodimer comprising two identical copies of the TACI-Fc fusion protein set forth in SEQ ID NO:170 linked by a covalent disulfide bond.

77. The immunomodulatory protein of any of claims 2, 49, 50, and 59-65, wherein the TACI-Fc fusion protein comprises the structure: (TACI)-Linker-Fc region-Linker-(TACI).

78. The immunomodulatory protein of any of claims 2, 49, 50, 59-65 and 77, wherein the TACI-Fc fusion protein is set forth in SEQ ID NO: 201.

79. The immunomodulatory protein of any of claims 2, 49, 50, 59-65 and 77, wherein the TACI-Fc fusion protein is set forth in SEQ ID NO: 202.

80. The immunomodulatory protein of any of claims 2, 49, 50, and 59-65, wherein the TACI-Fc fusion protein comprises the structure: (TACI)-Linker-(TACI)-Linker-Fc region.

81. The immunomodulatory protein of any of claims 2, 49, 50, 59-65 and 80, wherein the TACI-Fc fusion protein is set forth in SEQ ID NO: 198.

82. The immunomodulatory protein of any of claims 2, 49, 50, 59-65 and 77-81 that is a homodimer comprising two identical copies of the TACI-Fc fusion protein.

83. The immunomodulatory protein of any of claims 2, 49, 50 and 59-82, wherein the Fc fusion protein neutralizes APRIL and BAFF.

84. The immunomodulatory protein of any of claims 2, 49, 50 and 59-83, wherein:
the IC₅₀ for neutralizing APRIL is less than 100 pM, less than 50 pM, less than 40 pM, less than 30 pM, less than 20 pM, less than 10 pM, less than 5 pM or less than 1 pM, or is any value between any of the foregoing; and/or

the IC₅₀ for neutralizing BAFF is less than 400 pM, less than 300 pM, less than 200 pM, less than 100 pM, less than 75 pM, less than 50 pM, less than 25 pM, or less than 10 pM, or is any value between any of the foregoing.

85. The immunomodulatory protein of any of claims 1-84, wherein:
the Fc fusion protein blocks binding of APRIL, BAFF, or an APRIL/BAFF heterotrimer to BCMA or TACI; and/or
the Fc fusion protein reduces the levels of circulating APRIL, BAFF, or an APRIL/BAFF in the blood following administration to a subject.

86. The immunomodulatory protein of any of claims 1-85, wherein the immunomodulatory protein reduces or inhibits B cell maturation, differentiation and/or proliferation.

87. A nucleic acid molecule(s) encoding the immunomodulatory protein of any of claims 1-86.

88. A vector, comprising the nucleic acid molecule of claim 87.

89. The vector of claim 88 that is an expression vector.

90. The vector of claim 88 or claim 89, wherein the vector is a mammalian expression vector or a viral vector.

91. A cell, comprising the nucleic acid of claim 87 or the vector of any of any of claims 88-90.

92. The cell of claim 91 that is a mammalian cell.

93. The cell of claim 91 or claim 92 that is a human cell.

94. A method of producing an immunomodulatory protein, comprising introducing the nucleic acid molecule of claim 87 or vector of any of claims 88-90 into a host cell under conditions to express the protein in the cell.

95. The method of claim 94, further comprising isolating or purifying the immunomodulatory protein from the cell.
96. An immunomodulatory protein produced by the method of claim 94 or claim 95.
97. A pharmaceutical composition, comprising the immunomodulatory protein of any of claims 1-86 or claim 96.
98. The pharmaceutical composition of claim 97, comprising a pharmaceutically acceptable excipient.
99. An article of manufacture comprising the pharmaceutical composition of claim 97 or claim 98 in a vial or container.
100. A kit comprising the pharmaceutical composition of claim 97 or claim 98 or the article of manufacture of claim 99, and instructions for use.
101. A method of reducing an immune response in a subject, comprising administering the immunomodulatory protein of any of claims 1-86 or the pharmaceutical composition of claim 97 or claim 98 to a subject in need thereof.
102. The method of claim 101, wherein a B cell immune response is reduced in the subject, whereby B cell maturation, differentiation and/or proliferation is reduced or inhibited.
103. The method of claim 101 or claim 102, wherein circulating levels of APRIL, BAFF or an APRIL/BAFF heterotrimer are reduced in the subject.
104. The method of any of claims 101-103, wherein reducing the immune response treats a disease, disorder or condition in the subject.

105. A method of reducing circulating levels of APRIL, BAFF or an APRIL/BAFF heterotrimer in a subject comprising administering the immunomodulatory protein of any of claims 1-86 or the pharmaceutical composition of claim 97 or claim 98 to the subject.

106. A method of treating a disease, disorder or condition in a subject, comprising administering the immunomodulatory protein of any of claims 1-86 or the pharmaceutical composition of claim 97 or claim 98 to a subject in need thereof.

107. The method of claim 104 or claim 106, wherein the disease, disorder or condition is an autoimmune disease, and inflammatory condition, a B cell cancer, an antibody-mediated pathology, a renal disease, a graft rejection, graft versus host disease, or a viral infection.

108. The method of claim 106 or claim 107, wherein the disease, disorder or condition is selected from the group consisting of Systemic lupus erythematosus (SLE); Sjögren's syndrome, scleroderma, Multiple sclerosis, diabetes, polymyositis, primary biliary cirrhosis, IgA nephropathy, IgA vasculitis, optic neuritis, amyloidosis, antiphospholipid antibody syndrome (APS), autoimmune polyglandular syndrome type II (APS II), autoimmune thyroid disease (AITD), Graves' disease, autoimmune adrenalitis and pemphigus vulgaris.

109. The method of claim 106 or claim 107, wherein the disease, disorder or condition is a B cell cancer and the cancer is myeloma.

110. A pharmaceutical composition of claim 97 or claim 98 for use in reducing an immune response in a subject.

111. Use of an immunomodulatory protein of any of claims 1-86 or the pharmaceutical composition of claim 97 or claim 98 in the manufacture of a medicament for reducing an immune response in a subject.

112. The pharmaceutical composition for use of claim 110 or the use of claim 111, wherein the immune response is a B cell immune response, wherein reducing the immune response reduces or inhibits B cell maturation, differentiation and/or proliferation.

113. The pharmaceutical composition for use or the use of any of claims 110-112, wherein reducing the immune response reduces circulating levels of APRIL, BAFF or an APRIL/BAFF heterotrimer in the subject.

114. The pharmaceutical composition for use or the use of any of claims 110-113, wherein reducing the immune response treats a disease, disorder or condition in the subject.

115. A pharmaceutical composition of claim 97 or claim 98 for use in treating a disease, disorder or condition in a subject.

116. Use of an immunomodulatory protein of any of claims 1-86 or the pharmaceutical composition of claim 97 or claim 98 in the manufacture of a medicament for treating a disease, disorder or condition in a subject.

117. The pharmaceutical composition for use of claim 115 or the use of claim 116, wherein the disease, disorder or condition is an autoimmune disease, an inflammatory condition, a B cell cancer, an antibody-mediated pathology, a renal disease, a graft rejection, graft versus host disease, or a viral infection.

118. The pharmaceutical composition for use or the use of any of claims 115-117, wherein the disease, disorder or condition is selected from the group consisting of Systemic lupus erythematosus (SLE); Sjögren's syndrome, scleroderma, Multiple sclerosis, diabetes, polymyositis, primary biliary cirrhosis, IgA nephropathy, IgA vasculitis, optic neuritis, amyloidosis, antiphospholipid antibody syndrome (APS), autoimmune polyglandular syndrome type II (APS II), autoimmune thyroid disease (AITD), Graves' disease, autoimmune adrenalitis and pemphigus vulgaris.

119. The pharmaceutical composition for use or the use of any of claims 115-117, wherein the disease, disorder or condition is a B cell cancer and the cancer is myeloma.