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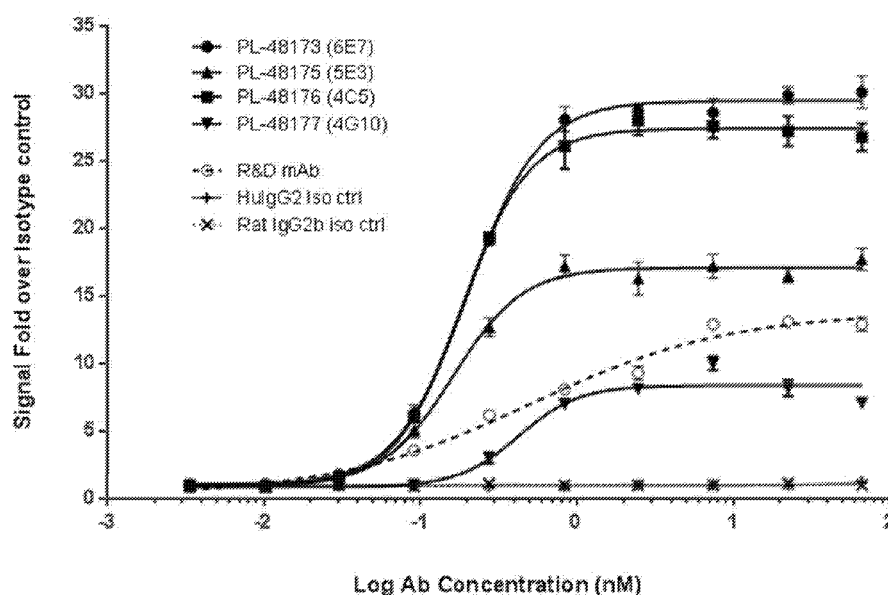


FIG. 1A

(57) Abstract: The present invention relates to antigen binding proteins, such as monoclonal antibodies, that specifically bind to and activate human triggering receptor expressed on myeloid cells-2 (TREM2) and pharmaceutical compositions comprising such antigen binding proteins. The agonist antigen binding proteins (e.g. antibodies) of the invention are capable of activating TREM2/DAP12 signaling in myeloid cells in the absence of Fc-mediated cross-linking of the antigen binding proteins. Methods of treating or preventing conditions associated with TREM2 loss of function, such as Alzheimer's disease and multiple sclerosis, using the antigen binding proteins are also described.



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TREM2 ANTIGEN BINDING PROTEINS AND USES THEREOF

FIELD OF THE INVENTION

[0001] The present invention relates to the field of biopharmaceuticals. In particular, the invention relates to antigen binding proteins, such as antibodies, that specifically bind to and activate human triggering receptor expressed on myeloid cells-2 (TREM2), pharmaceutical compositions comprising the antigen binding proteins, and methods of producing and using such antigen binding proteins.

SUBMISSION OF SEQUENCE LISTING ON ASCII TEXT FILE

[0002] The content of the following submission on ASCII text file is incorporated herein by reference in its entirety: a computer readable form (CRF) of the Sequence Listing (file name: A-2129-WO-PCT_Sequence_Listing_ST25, date created: April 18, 2018, size: 285,044 bytes).

BACKGROUND OF THE INVENTION

[0003] TREM2 is a member of the Ig superfamily of receptors that is expressed on cells of myeloid lineage, including macrophages, dendritic cells, and microglia (Schmid *et al.*, Journal of Neurochemistry, Vol. 83: 1309-1320, 2002; Colonna, Nature Reviews Immunology, Vol. 3: 445-453, 2003; Kiialainen *et al.*, Neurobiology of Disease, Vol. 18: 314-322, 2005). TREM2 is an orphan immune receptor with a short intracellular domain and functions by signaling through the adaptor protein DAP12, the cytoplasmic domain of which comprises an ITAM motif (Bouchon *et al.*, The Journal of Experimental Medicine, Vol. 194: 1111-1122, 2001). Upon activation of TREM2, tyrosine residues within the ITAM motif in DAP12 are phosphorylated by the Src family of kinases, providing docking sites for the tyrosine kinase ζ -chain-associated protein 70 (ZAP70) and spleen tyrosine kinase (Syk) via their SH2 domains (Colonna, Nature Reviews Immunology, Vol. 3: 445-453, 2003; Ulrich and Holtzman, ACS Chem. Neurosci., Vol. 7: 420-427, 2016). The ZAP70 and Syk kinases induce activation of several downstream signaling cascades, including phosphatidylinositol 3-kinase (PI3K), protein kinase C (PKC), extracellular regulated kinase (ERK), and elevation of intracellular calcium (Colonna, Nature Reviews Immunology, Vol. 3: 445-453, 2003; Ulrich and Holtzman, ACS Chem. Neurosci., Vol. 7: 420-427, 2016).

[0004] TREM2 has been implicated in several myeloid cell processes, including phagocytosis, proliferation, survival, and regulation of inflammatory cytokine production (Ulrich and Holtzman, ACS Chem. Neurosci., Vol. 7: 420-427, 2016). In the last few years, TREM2 has been linked to several diseases. For instance, mutations in both TREM2 and DAP12 have been linked to the autosomal recessive disorder Nasu-Hakola Disease, which is characterized by bone cysts, muscle wasting and demyelination phenotypes (Guerreiro *et al.*, New England Journal of Medicine, Vol. 368: 117-127, 2013). More recently, variants in the *TREM2* gene have been linked to increased risk for Alzheimer's disease (AD) and other forms of dementia including frontotemporal dementia (Jonsson *et al.*, New England Journal of Medicine, Vol. 368: 107-116, 2013; Guerreiro *et al.*, JAMA Neurology, Vol. 70:78-84, 2013; Jay *et al.*, Journal of Experimental Medicine, Vol. 212: 287-295, 2015). In particular, the R47H variant has been identified in genome-wide studies as being associated with increased risk for late-onset AD with an overall adjusted odds ratio (for populations of all ages) of 2.3, second only to the strong genetic association of ApoE to Alzheimer's. The R47H mutation resides on the extracellular Ig V-set domain of the TREM2 protein and has been shown to impact lipid binding and uptake of apoptotic cells and Abeta (Wang *et al.*, Cell, Vol. 160: 1061-1071, 2015; Yeh *et al.*, Neuron, Vol. 91: 328-340, 2016), suggestive of a loss-of-function linked to disease. Further, postmortem comparison of AD patients' brains with and without the R47H mutation are supportive of a novel loss-of-microglial barrier function for the carriers of the mutation, with the R47H carrier microglia putatively demonstrating a reduced ability to compact plaques and limit their spread (Yuan *et al.*, Neuron, Vol. 90: 724-739, 2016). Impairment in microgliosis has been reported in animal models of prion disease, multiple sclerosis, and stroke, suggesting that TREM2 may play an important role in supporting microgliosis in response to pathology or damage in the central nervous system (Ulrich and Holtzman, ACS Chem. Neurosci., Vol. 7: 420-427, 2016).

[0005] In view of the data indicating that deficits in TREM2 activity affect macrophage and microglia function and correlate with certain neurodegenerative disorders, there is a need in the art for therapeutic molecules that can induce or enhance TREM2-mediated functions.

SUMMARY OF THE INVENTION

[0006] The present invention is based, in part, on the design and generation of antigen binding proteins (e.g. antibodies) that specifically bind to and activate human TREM2 without the need for additional cross-linking. The agonist antigen binding proteins of the

invention are capable of activating TREM2/DAP12 signaling in myeloid cells in the absence of aggregation, clustering, and/or Fc-mediated cross-linking of the antigen binding proteins. Accordingly, in certain embodiments, the present invention provides isolated agonist antigen binding proteins that specifically bind to human TREM2 and induce or activate one or more TREM2-mediated functions.

[0007] In some embodiments, the TREM2 agonist antigen binding proteins increase phosphorylated Syk (pSyk) levels in the absence of a cross-linking agent in cells expressing TREM2. The cells may be cells of the myeloid lineage, including monocytes, dendritic cells, microglial cells, and macrophages. In certain embodiments, the TREM2 agonist antigen bindings increase pSyk levels in TREM2-expressing cells with an EC₅₀ less than 500 pM in the absence of a cross-linking agent as measured by a cell-based pSyk assay. In other embodiments, the TREM2 agonist antigen bindings increase pSyk levels in TREM2-expressing cells with an EC₅₀ less than 300 pM in the absence of a cross-linking agent as measured by a cell-based pSyk assay. In yet other embodiments, the TREM2 agonist antigen bindings increase pSyk levels in TREM2-expressing cells with an EC₅₀ from about 150 pM to about 500 pM in the absence of a cross-linking agent as measured by a cell-based pSyk assay.

[0008] The TREM2 agonist antigen binding proteins specifically bind to human TREM2 (SEQ ID NO: 1) or an extracellular domain (ECD) of human TREM2 (e.g. ECD set forth in SEQ ID NO: 2), for example with an equilibrium dissociation constant (K_D) less than 50 nM, less than 25 nM, less than 10 nM, or less than 5 nM. In certain embodiments, the TREM2 agonist antigen binding proteins do not cross-react with other TREM proteins, such as human TREM1. Thus, in one embodiment, the TREM2 agonist antigen binding proteins do not specifically bind to human TREM1 (SEQ ID NO: 4).

[0009] The TREM2 agonist antigen binding proteins of the invention can compete with any of the anti-TREM2 antibodies described herein (e.g. antibodies listed in Tables 1A, 1B, 2A, 2B, 3A and 3B) for binding to human TREM2. In one embodiment, the TREM2 agonist antigen binding protein competes with a reference antibody for binding to human TREM2, wherein the reference antibody comprises a light chain variable region comprising the sequence of SEQ ID NO: 61 and a heavy chain variable region comprising the sequence of SEQ ID NO: 124. In another embodiment, the TREM2 agonist antigen binding protein competes with a reference antibody for binding to human TREM2, wherein the reference antibody comprises a light chain variable region comprising the sequence of SEQ ID NO: 62

and a heavy chain variable region comprising the sequence of SEQ ID NO: 125. In yet another embodiment, the TREM2 agonist antigen binding protein competes with a reference antibody for binding to human TREM2, wherein the reference antibody comprises a light chain variable region comprising the sequence of SEQ ID NO: 52 and a heavy chain variable region comprising the sequence of SEQ ID NO: 115. In still another embodiment, the TREM2 agonist antigen binding protein competes with a reference antibody for binding to human TREM2, wherein the reference antibody comprises a light chain variable region comprising the sequence of SEQ ID NO: 56 and a heavy chain variable region comprising the sequence of SEQ ID NO: 119.

[0010] In certain embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3. The light chain and heavy chain variable regions or CDRs may be from any of the anti-TREM2 antibodies described herein or a variant thereof. For instance, in some embodiments, the TREM2 agonist antigen binding proteins comprise a CDRL1 comprising a sequence selected from SEQ ID NOs: 5-18 or a variant thereof having one, two, three or four amino acid substitutions; a CDRL2 comprising a sequence selected from SEQ ID NOs: 19-30 or a variant thereof having one, two, three or four amino acid substitutions; a CDRL3 comprising a sequence selected from SEQ ID NOs: 31-45 or a variant thereof having one, two, three or four amino acid substitutions; a CDRH1 comprising a sequence selected from SEQ ID NOs: 77-86 or a variant thereof having one, two, three or four amino acid substitutions; a CDRH2 comprising a sequence selected from SEQ ID NOs: 87-94 or a variant thereof having one, two, three or four amino acid substitutions; and a CDRH3 comprising a sequence selected from SEQ ID NOs: 95-109 or a variant thereof having one, two, three or four amino acid substitutions.

[0011] In some embodiments, the TREM2 agonist antigen binding proteins comprise a light chain variable region comprising a sequence selected from SEQ ID NOs: 46-63 and a heavy chain variable region comprising a sequence selected from SEQ ID NOs: 110-126. In one embodiment, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising the sequence of SEQ ID NO: 54 and a heavy chain variable region comprising the sequence of SEQ ID NO: 117. In another embodiment, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising the sequence of SEQ ID NO: 55 and a heavy chain variable region comprising the sequence of SEQ ID NO:

118. In another embodiment, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising the sequence of SEQ ID NO: 60 and a heavy chain variable region comprising the sequence of SEQ ID NO: 123. In still another embodiment, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising the sequence of SEQ ID NO: 61 and a heavy chain variable region comprising the sequence of SEQ ID NO: 124. In another embodiment, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising the sequence of SEQ ID NO: 62 and a heavy chain variable region comprising the sequence of SEQ ID NO: 125. In yet another embodiment, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising the sequence of SEQ ID NO: 52 and a heavy chain variable region comprising the sequence of SEQ ID NO: 115.

[0012] In some embodiments, the TREM2 agonist antigen binding proteins comprise a light chain variable region that is derived from a light chain variable region from any of the anti-TREM2 antibodies described herein. Thus, in some embodiments, the light chain variable region of the TREM2 agonist antigen binding proteins comprises a sequence that is at least 90% identical, at least 91% identical, at least 92% identical, at least 93% identical, at least 94% identical, or at least 95% identical to a sequence selected from SEQ ID NOs: 46-63. For instance, the TREM2 agonist antigen binding proteins can comprise a light chain variable region from any of the engineered anti-TREM2 antibody variants set forth in Tables 13-18. In one embodiment, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising the sequence of SEQ ID NO: 54 with a mutation at one or more amino acid positions 64, 79, 80, 85, 94, and/or 100. In some such embodiments, the mutation is V64G, V64A, Q79E, Q79D, S80P, S80A, F85V, F85L, F85A, F85D, F85I, F85L, F85M, F85T, W94F, W94Y, W94S, W94T, W94A, W94H, W94I, W94Q, P100R, P100Q, P100G, or combinations thereof. In another embodiment, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising the sequence of SEQ ID NO: 55 with a mutation at one or more amino acid positions 64, 79, 80, 94, and/or 100. Such mutations can include V64G, V64A, Q79E, Q79D, S80P, S80A, W94F, W94Y, W94S, W94T, W94A, W94H, W94I, W94Q, P100R, P100Q, P100G, or combinations thereof. In certain embodiments, the mutation is V64G, V64A, Q79E, S80P, S80A, W94Y, W94S, P100R, P100Q, or combinations thereof. In another embodiment, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising the sequence of SEQ ID NO: 60 with a mutation at one or more amino acid positions 60, 92, and/or 93. The mutation in such

embodiments can be selected from L60S, L60P, L60D, L60A, D92E, D92Q, D92T, D92N, S93A, S93N, S93Q, S93V, or combinations thereof. In yet another embodiment, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising the sequence of SEQ ID NO: 61 with a mutation at one or more amino acid positions 56, 57, 92, and/or 93. In such embodiments, the mutation can be N56S, N56T, N56Q, N56E, G57A, G57V, D92E, D92Q, D92T, D92N, S93A, S93N, S93Q, S93V, or combinations thereof. In certain embodiments, the mutation is N56S, N56Q, G57A, D92E, D92Q, S93A, or combinations thereof. In still another embodiment, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising the sequence of SEQ ID NO: 62 with a mutation at amino acid position 36, 46, 61 and/or 100. Such mutations can include F36Y, S46L, S46R, S46V, S46F, K61R, P100Q, P100G, P100R or combinations thereof. In particular embodiments, the mutation is F36Y, K61R, P100Q, or combinations thereof. In another embodiment, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising the sequence of SEQ ID NO: 52 with a mutation at amino acid position 91, which can be selected from F91V, F91I, F91T, F91L, or F91D. In one embodiment, the mutation is F91V.

[0013] In certain embodiments, the TREM2 agonist antigen binding proteins comprise a heavy chain variable region that is derived from a heavy chain variable region from any of the anti-TREM2 antibodies described herein. Thus, in some embodiments, the heavy chain variable region of the TREM2 agonist antigen binding proteins comprises a sequence that is at least 90% identical, at least 91% identical, at least 92% identical, at least 93% identical, at least 94% identical, or at least 95% identical to a sequence selected from SEQ ID NOs: 110-126. For instance, the TREM2 agonist antigen binding proteins can comprise a heavy chain variable region from any of the engineered anti-TREM2 antibody variants set forth in Tables 13-18. In one embodiment, the TREM2 agonist antigen binding protein comprises a heavy chain variable region comprising the sequence of SEQ ID NO: 117 with a mutation at one or more amino acid positions 19, 55, 56, 57, 58, and/or 104. In some such embodiments, the mutation is M19K, M19R, M19T, M19E, M19N, M19Q, D55E, D55Q, D55N, D55T, S56A, S56Q, S56V, D57S, D57E, D57Q, T58A, T58V, W104F, W104Y, W104T, W104S, W104A, W104H, W104I, W104Q, or combinations thereof. In another embodiment, the TREM2 agonist antigen binding protein comprises a heavy chain variable region comprising the sequence of SEQ ID NO: 118 with a mutation at one or more amino acid positions 19, 55, 56, 57, 58, and/or 104. Such mutations can include M19K, M19R, M19T, M19E, M19N, M19Q,

D55E, D55Q, D55N, D55T, S56A, S56Q, S56V, D57S, D57E, D57Q, T58A, T58V, W104F, W104Y, W104T, W104S, W104A, W104H, W104I, W104Q, or combinations thereof. In certain embodiments, the mutation is M19K, D55E, S56A, D57E, T58A, W104Y, W104T, or combinations thereof. In another embodiment, the TREM2 agonist antigen binding protein comprises a heavy chain variable region comprising the sequence of SEQ ID NO: 123 with a mutation at one or more amino acid positions 27, 55, 56, 57, 58, 105, and/or 106. In some embodiments, the mutation is selected from H27Y, H27D, H27F, H27N, D55E, D55Q, D55N, D55T, S56A, S56Q, S56V, D57S, D57E, D57Q, T58A, T58V, D105E, D105Q, D105T, D105N, D105G, S106A, S106Q, S106V, S106T, or combinations thereof. In yet another embodiment, the TREM2 agonist antigen binding protein comprises a heavy chain variable region comprising the sequence of SEQ ID NO: 124 with a mutation at one or more amino acid positions 55, 56, 57, 58, 105, and/or 106. The mutation in such embodiments can be selected from D55E, D55Q, D55N, D55T, S56A, S56Q, S56V, D57S, D57E, D57Q, T58A, T58V, D105E, D105Q, D105T, D105N, D105G, S106A, S106Q, S106V, S106T, or combinations thereof. In certain embodiments, the mutation is D55E, D55Q, S56A, D57E, T58A, D105E, D105N, S106A, or combinations thereof. In still another embodiment, the TREM2 agonist antigen binding protein comprises a heavy chain variable region comprising the sequence of SEQ ID NO: 125 with a mutation at one or more amino acid positions 43, 76, 85, 99, 100, and/or 116. Such mutations can include L43Q, L43K, L43H, I76T, R85S, R85G, R85N, R85D, D99E, D99Q, D99S, D99T, G100A, G100Y, G100V, T116L, T116M, T116P, T116R, or combinations thereof. In certain embodiments, the mutation is L43Q, R85S, D99E, G100A, G100Y, T116L, or combinations thereof. In another embodiment, the TREM2 agonist antigen binding protein comprises a heavy chain variable region comprising the sequence of SEQ ID NO: 115 with a mutation at amino acid position 62 and/or 63. In such embodiments, the mutation can be selected from D62E, D62Q, D62T, D62N, S63A, S63Q, S63V, or combinations thereof. In some embodiments, the mutation is D62E, D62Q, S63A, or combinations thereof.

[0014] In some embodiments, the TREM2 agonist antigen binding proteins comprise one or more CDRs of a variant of the anti-TREM2 antibodies described herein. For instance, the TREM2 agonist antigen binding proteins may comprise one or more CDRs of the anti-TREM2 antibody variants set forth in Tables 2A, 2B, 3A, 3B, and 19. In certain embodiments, the TREM2 agonist antigen binding proteins comprise one or more CDRs of anti-TREM2 antibody variants with improved binding affinity. In these and other

embodiments, the TREM2 agonist antigen binding proteins comprise a CDRL1 comprising the sequence of SEQ ID NO: 16; a CDRL2 comprising a CDRL2 consensus sequence; a CDRL3 comprising a CDRL3 consensus sequence; a CDRH1 comprising the sequence of SEQ ID NO: 85, a CDRH2 comprising a CDRH2 consensus sequence; and a CDRH3 comprising a CDRH3 consensus sequence. In one embodiment, the CDRL2 consensus sequence is $X_1ASSX_2QX_3$ (SEQ ID NO: 139), where X_1 is A or G; X_2 is L or R; and X_3 is N, K, R, L, or T. In related embodiments, the CDRL3 consensus sequence is $X_1QADX_2X_3PX_4T$ (SEQ ID NO: 140), where X_1 is Q or G; X_2 is S or R; X_3 is F, L, or Y; and X_4 is R or H. In these and other embodiments, the CDRH2 consensus sequence is $X_1IYPGSDSX_2RX_3X_4PX_5FQX_6$ (SEQ ID NO: 141), where X_1 is I or T; X_2 is T or V; X_3 is Y or L; X_4 is S or A; X_5 is S, G, or E; and X_6 is G or D. The CDRH3 consensus may be $X_1RTFYDSSDYX_2DY$ (SEQ ID NO: 142), where X_1 is Q, G, S, or M; and X_2 is F or S. In further embodiments, the CDRL2 of the TREM2 agonist antigen binding proteins of the invention may comprise a sequence selected from SEQ ID NOs: 26 and 143-147. In still further embodiments, the CDRL3 of the TREM2 agonist antigen binding proteins of the invention may comprise a sequence selected from SEQ ID NOs: 43 and 148-152. In some embodiments, the CDRH2 of the TREM2 agonist antigen binding proteins of the invention may comprise a sequence selected from SEQ ID NOs: 91 and 170-175. In other embodiments, the CDRH3 of the TREM2 agonist antigen binding proteins of the invention may comprise a sequence selected from SEQ ID NOs: 176-179.

[0015] In other embodiments, the TREM2 agonist antigen binding proteins comprise one or more CDRs of anti-TREM2 antibody variants with reduced binding affinity. In these and other embodiments, the TREM2 agonist antigen binding proteins comprise a CDRL1 comprising a CDRL1 consensus sequence; a CDRL2 comprising a CDRL2 consensus sequence; a CDRL3 comprising a CDRL3 consensus sequence; a CDRH1 comprising a CDRH1 consensus sequence, a CDRH2 comprising a CDRH2 consensus sequence; and a CDRH3 comprising a CDRH3 consensus sequence. In one embodiment, the CDRL1 consensus sequence is $X_1ASQGISX_2WLA$ (SEQ ID NO: 284), where X_1 is R or A; and X_2 is S or R. In related embodiments, the CDRL2 consensus sequence is X_1AX_2SLQN (SEQ ID NO: 285), where X_1 is A or S; and X_2 is S or G. In other related embodiments, the CDRL3 consensus sequence is $QQAX_1SFPX_2T$ (SEQ ID NO: 286), where X_1 is D or V; and X_2 is R or L. In these and other embodiments, the CDRH1 consensus sequence is SX_1WIA (SEQ ID NO: 287), where X_1 is Y or E. In related embodiments, the CDRH2 consensus sequence is

IIYPX₁DS DTRYSPSFQG (SEQ ID NO: 288), where X₁ is G or S. The CDRH3 consensus may be QRX₁FX₂X₃DSSDYFDY (SEQ ID NO: 289), where X₁ is T or G; X₂ is Y or R; and X₃ is Y or G. In some embodiments, the CDRL1 of the TREM2 agonist antigen binding proteins of the invention may comprise a sequence selected from SEQ ID NOs: 16, 290, and 291. In further embodiments, the CDRL2 of the TREM2 agonist antigen binding proteins of the invention may comprise a sequence selected from SEQ ID NOs: 28, 292, and 293. In still further embodiments, the CDRL3 of the TREM2 agonist antigen binding proteins of the invention may comprise a sequence selected from SEQ ID NOs: 43, 294, and 271. In some embodiments, the CDRH1 of the TREM2 agonist antigen binding proteins of the invention may comprise the sequence of SEQ ID NO: 85 or SEQ ID NO: 302. In other embodiments, the CDRH2 of the TREM2 agonist antigen binding proteins of the invention may comprise the sequence of SEQ ID NO: 91 or SEQ ID NO: 303. In still other embodiments, the CDRH3 of the TREM2 agonist antigen binding proteins of the invention may comprise a sequence selected from SEQ ID NOs: 107 and 304-306.

[0016] In certain embodiments, the TREM2 agonist antigen binding proteins comprise a light chain variable region and/or heavy chain variable region from any of the anti-TREM2 variant antibodies set forth in Tables 2A, 2B, 3A, 3B, and 19. Accordingly, in some embodiments, the light chain variable region of the TREM2 agonist antigen binding proteins comprises a sequence that is at least 90% identical, at least 91% identical, at least 92% identical, at least 93% identical, at least 94% identical, or at least 95% identical to a sequence selected from SEQ ID NOs: 61, 153-162, and 295-300. In these and other embodiments, the heavy chain variable region of the TREM2 agonist antigen binding proteins comprises a sequence that is at least 90% identical, at least 91% identical, at least 92% identical, at least 93% identical, at least 94% identical, or at least 95% identical to a sequence selected from SEQ ID NOs: 124, 180-190, and 307-312.

[0017] In any of the embodiments described herein, including the embodiments described above, the TREM2 agonist antigen binding protein is an antibody or binding fragment thereof, preferably a monoclonal antibody or binding fragment thereof. In some embodiments, the monoclonal antibody or binding fragment thereof is a chimeric antibody or binding fragment thereof. In other embodiments, the monoclonal antibody or binding fragment thereof is a humanized antibody or binding fragment thereof. In yet other embodiments, the monoclonal antibody or binding fragment thereof is a fully human antibody or binding fragment thereof. The monoclonal antibody can be of any isotype, such

as a human IgG1, IgG2, IgG3, or IgG4. In one particular embodiment, the monoclonal antibody is a human IgG1 antibody. In another particular embodiment, the monoclonal antibody is a human IgG2 antibody.

[0018] In certain embodiments in which the TREM2 agonist antigen binding protein is an antibody (e.g. monoclonal antibody), the antibody may contain one or more modifications that affect the glycosylation of the antibody. In some embodiments, the antibody comprises one or more mutations to reduce or eliminate glycosylation. In such embodiments, the aglycosylated antibody may comprise a mutation at amino acid position N297 (according to the EU numbering scheme), such as a N297G mutation, in its heavy chain. The aglycosylated antibody may comprise further mutations to stabilize the antibody structure. Such mutations can include pairs of cysteine substitutions, such as A287C and L306C, V259C and L306C, R292C and V302C, and V323C and I332C (amino acid positions according to the EU numbering scheme). In one embodiment, the aglycosylated antibody comprises R292C and V302C mutations (according to the EU numbering scheme) in its heavy chain. In certain embodiments, the aglycosylated anti-TREM2 agonist antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 202 or SEQ ID NO: 203.

[0019] In further embodiments in which the TREM2 agonist antigen binding protein is a human IgG2 antibody (e.g. monoclonal antibody) or comprises a CH1 region and hinge region from a human IgG2 antibody, the antibody may contain one or more modifications that affect the hinge structure of the antibody. In one such embodiment, the anti-TREM2 agonist antibody comprises a C131S mutation (according to the EU numbering scheme) in its heavy chain. In another embodiment, the anti-TREM2 agonist antibody comprises a C214S mutation (according to the EU numbering scheme) in its light chain and a C219S mutation (according to the EU numbering scheme) in its heavy chain. In another embodiment, the anti-TREM2 agonist antibody comprises a C214S mutation (according to the EU numbering scheme) in its light chain and a C220S mutation (according to the EU numbering scheme) in its heavy chain.

[0020] In certain embodiments, the TREM2 agonist antigen binding proteins of the invention may comprise a CH1 region and hinge region from a human IgG2 antibody (e.g. the amino acid of SEQ ID NO: 207), and an Fc region from a human IgG1 antibody. In one embodiment, the TREM2 agonist antigen binding protein comprises a CH1 region and hinge region from a human IgG2 antibody (e.g. the amino acid sequence of SEQ ID NO: 207) and

an Fc region from a human IgG1 antibody, wherein the Fc region comprises the amino acid sequence of SEQ ID NO: 281.

[0021] In certain embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain comprising a light chain variable region and a heavy chain comprising a heavy chain variable region, wherein: (a) the light chain variable region having the amino acid sequence of SEQ ID NO: 326, and the heavy chain variable region having the amino acid sequence of SEQ ID NO: 327; (b) the light chain variable region having the amino acid sequence of SEQ ID NO: 328, and the heavy chain variable region having the amino acid sequence of SEQ ID NO: 329; (c) the light chain variable region having the amino acid sequence of SEQ ID NO: 330, and the heavy chain variable region having the amino acid sequence of SEQ ID NO: 331; or (d) the light chain variable region having the amino acid sequence of SEQ ID NO: 332, and the heavy chain variable region having the amino acid sequence of SEQ ID NO: 333. In certain embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain and a heavy chain, wherein: (a) the light chain having the amino acid sequence of SEQ ID NO: 334, and the heavy chain having the amino acid sequence of SEQ ID NO: 335; (b) the light chain having the amino acid sequence of SEQ ID NO: 334, and the heavy chain having the amino acid sequence of SEQ ID NO: 336; (c) the light chain having the amino acid sequence of SEQ ID NO: 337, and the heavy chain having the amino acid sequence of SEQ ID NO: 338; (d) the light chain having the amino acid sequence of SEQ ID NO: 339, and the heavy chain having the amino acid sequence of SEQ ID NO: 340; or (e) the light chain having the amino acid sequence of SEQ ID NO: 341, and the heavy chain having the amino acid sequence of SEQ ID NO: 342.

[0022] The present invention also provides polynucleotides and expression vectors encoding the TREM2 agonist antigen binding proteins described herein as well as host cells, such as CHO cells, comprising the encoding polynucleotides and expression vectors. In certain embodiments, the present invention includes methods for producing the TREM2 agonist antigen binding proteins, including anti-TREM2 agonist monoclonal antibodies and binding fragments thereof. In one embodiment, the method comprises culturing a host cell comprising an expression vector encoding the antigen binding protein under conditions that allow expression of the antigen binding protein, and recovering the antigen binding protein from the culture medium or host cell.

[0023] The TREM2 agonist antigen binding proteins described herein can be used in the manufacture of a pharmaceutical composition or medicament for the treatment or prevention

of conditions associated with TREM2 deficiency or loss of TREM2 biological activity, such as Alzheimer's disease, Nasu-Hakola disease, frontotemporal dementia, multiple sclerosis, prion disease, or stroke. Thus, the present invention also provides a pharmaceutical composition comprising a TREM2 agonist antigen binding protein described herein and a pharmaceutically acceptable excipient.

[0024] In certain embodiments, the present invention provides methods for treating, preventing, or reducing the risk of developing conditions associated with TREM2 deficiency or loss of TREM2 biological activity in a patient in need thereof. In one embodiment, the method comprises administering to the patient an effective amount of any of the TREM2 agonist antigen binding proteins described herein. In some embodiments, the condition to be treated, prevented, or ameliorated is Alzheimer's disease. In other embodiments, the condition to be treated, prevented, or ameliorated is multiple sclerosis. The patient in need of treatment may be determined to have one or more genotypes associated with an increased risk of developing a disease or condition that can be treated according to the methods of the invention. For instance, in some embodiments, the patient has a genotype associated with an increased risk of developing Alzheimer's disease, such as the genotypes described herein. In further embodiments, the patient may be determined to carry an allele encoding a TREM2 variant associated with an increased risk of developing Alzheimer's disease. Such variants can include the R47H TREM2 variant and the R62H TREM2 variant.

[0025] The present invention also includes methods of increasing survival or proliferation of myeloid cells, such as macrophages, microglia, and dendritic cells, in a patient in need thereof. In one embodiment, the method comprises administering to the patient an effective amount of any of the TREM2 agonist antigen binding proteins described herein. In some embodiments, the patient in need of treatment is at risk for, suffers from, or has been diagnosed with a neurodegenerative disorder, such as Alzheimer's disease. In other embodiments, the patient in need of treatment is at risk for, suffers from, or has been diagnosed with an autoimmune disorder, such as multiple sclerosis.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] **Figure 1A** depicts dose-response curves for agonist activity of purified monoclonal human anti-TREM2 antibodies from harvest 1. The fold-increase in phosphorylated Syk (pSyk) levels in HEK293T cells expressing human TREM2/DAP12 is plotted as a function of concentration of human anti-TREM2 antibodies. Agonist activity of a commercially available

rat anti-human/mouse TREM2 antibody (mAb17291; “R&D mAb” or “Antibody 1”) is included for comparison. Human IgG2 and rat IgG2b isotype antibodies were used as controls.

[0027] **Figure 1B** depicts dose-response curves for agonist activity of unpurified monoclonal human anti-TREM2 antibodies from hybridoma supernatants from harvests 3, 4, and 5. The fold-increase in pSyk levels in HEK293T cells expressing human TREM2/DAP12 is plotted as a function of concentration of human anti-TREM2 antibodies. Human IgG2 isotype antibody was used as a control.

[0028] **Figures 2A and 2B** are sequence alignments of kappa light chain variable regions of exemplary anti-TREM2 antibodies to original germline sequences. Figure 2B is a continuation of the sequences in Figure 2A.

[0029] **Figures 3A and 3B** are sequence alignments of lambda light chain variable regions of exemplary anti-TREM2 antibodies to original germline sequences. Figure 3B is a continuation of the sequences in Figure 3A.

[0030] **Figures 4A and 4B** are sequence alignments of heavy chain variable regions of exemplary anti-TREM2 antibodies to original germline sequences. Figure 4B is a continuation of the sequences in Figure 4A.

[0031] **Figure 5** is a plot of binding signal as a function of time of an anti-human Fc kinetic sensor (Octet® HTX instrument; Pall ForteBio) loaded with the 6E7 antibody at the time indicated by the dotted line (“1st Ab capture”). The first solid denotes the time at which an irrelevant human IgG2 antibody was added to the sensor to reduce non-specific binding events (“Sensor blocking with G2”). The second solid line denotes the time at which the target antigen (soluble human TREM2) was added to the sensor to interact with the captured 6E7 antibody. The final solid line indicates the time at which the sandwich antibody (5E3, 6E7, or a control IgG2 antibody) was added to the sensor. An increase in binding is observed when the 5E3 antibody is added, which suggests that the 5E3 antibody binds to a different epitope on human TREM2 from the epitope bound by the 6E7 antibody.

[0032] **Figure 6** depicts a dose-response curve for agonist activity of monoclonal human anti-TREM2 antibodies (4C5, 4G10, 5E3, 6E7, 10E3, 13E7, 24G6, 16B8, 25F12, 26F2, 32E3, and 33B12) in differentiated THP-1 cells. The fold-increase in phosphorylated Syk (pSyk) levels over baseline is plotted as a function of concentration of human anti-TREM2 antibodies. Human IgG2 (HuIgG) and rat IgG2b (RtIgG) isotype antibodies were used as

controls. Agonist activity of a commercially available rat anti-human/mouse TREM2 antibody (mAb17291; “RnD”) is included for comparison.

[0033] **Figure 7** depicts dose-response curves for agonist activity of purified 6E7 and 5E3 human anti-TREM2 antibodies in an IgG2 (“G2”), IgG1 (“G1”) or an aglycosylated IgG1 (“SEFL2”) format. The fold-increase in phosphorylated Syk (pSyk) levels over the corresponding isotype control in HEK293T cells expressing human TREM2/DAP12 is plotted as a function of concentration of the human anti-TREM2 antibodies. Conversion of the 6E7 and 5E3 antibodies from an IgG2 isotype to an IgG1 isotype results in the partial loss of agonist activity.

[0034] **Figure 8A** is a bar graph of numbers of bone marrow derived macrophages (BMDMs) derived from wild-type (TREM^{+/+}) and TREM2^{-/-} mice in different days of culture under limiting conditions of CSF-1. The TREM2^{-/-} BMDMs exhibit a survival defect in these culture conditions.

[0035] **Figure 8B** is a bar graph of percent cell confluence of mouse adult microglia derived from wild-type (TREM^{+/+}) and TREM2^{-/-} mice at different time points in culture under limiting conditions of CSF-1. TREM2^{-/-} mouse adult microglia exhibit a survival defect in these culture conditions.

[0036] **Figure 8C** is a bar graph of percent cell confluence of mouse neonatal microglia derived from wild-type (TREM^{+/+}) and TREM2^{-/-} mice at different time points in culture under limiting conditions of CSF-1. Neonatal TREM2^{-/-} microglia exhibit a survival defect over time.

[0037] **Figure 8D** is a bar graph of numbers of BMDMs derived from wild-type (TREM^{+/+}) and TREM2^{R47H} mice in different days of culture under limiting conditions of CSF-1. TREM2^{R47H} mouse BMDMs exhibit a survival defect in these culture conditions.

[0038] **Figure 8E** is a bar graph of percent cell confluence of mouse adult microglia derived from wild-type (TREM^{+/+}) and TREM2^{R47H} mice at different time points in culture under limiting conditions of CSF-1. TREM2^{R47H} mouse adult microglia exhibit a survival defect in these culture conditions.

[0039] **Figure 8F** is a bar graph of percent cell confluence of mouse neonatal microglia derived from wild-type (TREM^{+/+}) and TREM2^{R47H} mice at different time points in culture under limiting conditions of CSF-1. Neonatal TREM2^{R47H} microglia exhibit a survival defect that increases over time.

[0040] **Figure 9A** is a western blot of cell lysates from TREM2^{R47H} and wild-type (TREM2^{+/+}) BMDMs treated with an anti-TREM2 antibody or an isotype control. The anti-TREM2 antibody activates TREM2/DAP12 signaling in both types of macrophage as indicated by the increase in pSyk levels.

[0041] **Figure 9B** is a western blot of cell lysates from TREM2^{-/-} and wild-type (TREM2^{+/+}) BMDMs treated with an anti-TREM2 antibody or an isotype control. The anti-TREM2 antibody does not increase pSyk levels in the TREM2^{-/-} BMDMs confirming that the effect is specific for TREM2.

[0042] **Figure 10A** is a graph depicting percent cell confluence over time for TREM2^{R47H} BMDMs treated with an isotype control antibody or an anti-TREM2 agonist antibody as measured by a real-time cell confluence assay. Data are plotted as mean +/- s.d. and are from a single representative experiment. The experiment was conducted twice independently (n=2 and assayed in triplicate).

[0043] **Figure 10B** is a graph depicting percent cell confluence over time for wild-type (TREM2^{+/+}) BMDMs treated with an isotype control antibody or an anti-TREM2 agonist antibody as measured by a real-time cell confluence assay. Data are plotted as mean +/- s.d. and are from a single representative experiment. The experiment was conducted twice independently (n=2 and assayed in triplicate).

[0044] **Figure 10C** is a bar graph depicting cell viability as measured by CellTiter Glo ATP detection assay for TREM2^{R47H} and TREM2^{+/+} BMDMs treated with vehicle, isotype control, or an anti-TREM2 agonist antibody for 14 days.

[0045] **Figure 10D** is a bar graph depicting percent cell confluence at particular times in culture for TREM2^{R47H} adult mouse microglia treated with an isotype control antibody or an anti-TREM2 agonist antibody. An increase in survival of TREM2^{R47H} microglia is observed with anti-TREM2 agonist antibody treatment.

[0046] **Figure 10E** is a graph depicting percent cell confluence over time for BMDMs harvested from aged (18-month old) wildtype (TREM2^{+/+}) mice (n=3 animals) treated with an isotype control antibody or an anti-TREM2 agonist antibody of the present invention (henceforth referred to as "Antibody 2") as measured by a real-time cell confluence assay. Data are plotted as mean +/- s.d. and are from a single representative experiment.

****p<.0001, 2-way ANOVA with Sidak's correction for multiple comparisons. **Figure 10F** is a graph depicting percent cell confluence over time for BMDMs harvested from aged (18-month old) TREM2^{R47H} mice (n=3 animals, exception -- wild-type age-matched littermate

controls for day 6 samples in the knockout experiment) treated with an isotype control antibody or an anti-TREM2 agonist antibody (Antibody 2) as measured by a real-time cell confluence assay. Data are plotted as mean $\pm$ s.d. and are from a single representative experiment. **** $p < .0001$, 2-way ANOVA with Sidak's correction for multiple comparisons. An increase in survival of wildtype and TREM2^{R47H} macrophages is observed with anti-TREM2 agonist antibody treatment.

[0047] **Figure 11A** is a graph depicting percent cell confluence over time in a culture compartment in a migration assay for wild-type (TREM2^{+/+}) BMDMs treated with an isotype control antibody or an anti-TREM2 agonist antibody (Antibody 1) as measured by a real-time cell confluence assay. The anti-TREM2 agonist antibody had minimal effects on migration of the wild-type BMDMs in this assay.

[0048] **Figure 11B** is a graph depicting percent cell confluence over time in a culture compartment in a migration assay for TREM2^{R47H} BMDMs treated with an isotype control antibody or an anti-TREM2 agonist antibody (Antibody 1) as measured by a real-time cell confluence assay. The anti-TREM2 agonist antibody resulted in a small but statistically significant reduction of migration of the TREM2^{R47H} BMDMs in this assay.

[0049] **Figure 11C** is a graph depicting percent cell confluence over time in a culture compartment in a migration assay for TREM2^{-/-} BMDMs treated with an isotype control antibody or an anti-TREM2 agonist antibody (Antibody 1) as measured by a real-time cell confluence assay. The anti-TREM2 agonist antibody has no effect on the migration of the TREM2^{-/-} BMDMs in this assay.

[0050] **Figure 11D and Figure 11E** are graphs depicting percent cell confluence over time in a culture compartment in a migration assay for wildtype (TREM2^{+/+}) and TREM2^{R47H} BMDMs, respectively, treated with an isotype control antibody or an anti-TREM2 agonist antibody (Antibody 2) as measured by a real-time cell confluence assay. The anti-TREM2 agonist antibody treatment has no effect on the migration of the wildtype and TREM2^{R47H} BMDMs in this assay.

[0051] **Figure 12A** shows the differential regulation of CDC20 transcripts as measured by qPCR in wild-type (TREM2^{+/+}), TREM2^{R47H}, and TREM2^{-/-} macrophages at day 5 and day 6.

[0052] **Figure 12B** shows the differential regulation of PKB transcripts as measured by qPCR in wild-type (TREM2^{+/+}), TREM2^{R47H}, and TREM2^{-/-} macrophages at day 5 and day 6.

[0053] **Figure 12C** shows the differential regulation of NDC80 transcripts as measured by qPCR in wild-type (TREM2^{+/+}), TREM2^{R47H}, and TREM2^{-/-} macrophages at day 5 and day 6.

[0054] **Figure 12D** shows the differential regulation of CCR2 transcripts as measured by qPCR in wild-type (TREM2^{+/+}), TREM2^{R47H}, and TREM2^{-/-} macrophages at day 5 and day 6.

[0055] **Figure 13A** depicts the differential regulation of ApoE transcripts as measured by qPCR in wild-type (TREM2^{+/+}), heterozygous (TREM2^{+/-}), and knockout (TREM2^{-/-}) macrophages at different time points in culture. All gene expression levels are normalized to wild-type control macrophages at Day 4 of culture.

[0056] **Figure 13B** depicts the differential regulation of ApoE transcripts as measured by qPCR in wild-type (TREM2^{+/+}), R47H heterozygous (TREM2^{R47H/+}), and R47H homozygous (TREM2^{R47H}) macrophages at different time points in culture. All gene expression levels are normalized to wild-type control macrophages at Day 4 of culture.

[0057] **Figure 13C** depicts the differential regulation of IL-1a transcripts as measured by qPCR in wild-type (TREM2^{+/+}), heterozygous (TREM2^{+/-}), and knockout (TREM2^{-/-}) macrophages at different time points in culture. All gene expression levels are normalized to wild-type control macrophages at Day 4 of culture.

[0058] **Figure 13D** depicts the differential regulation of IL-1a transcripts as measured by qPCR in wild-type (TREM2^{+/+}), R47H heterozygous (TREM2^{R47H/+}), and R47H homozygous (TREM2^{R47H}) macrophages at different time points in culture. All gene expression levels are normalized to wild-type control macrophages at Day 4 of culture.

[0059] **Figure 13E** depicts the differential regulation of CX3CR1 transcripts as measured by qPCR in wild-type (TREM2^{+/+}), heterozygous (TREM2^{+/-}), and knockout (TREM2^{-/-}) macrophages at different time points in culture. All gene expression levels are normalized to wild-type control macrophages at Day 4 of culture.

[0060] **Figure 13F** depicts the differential regulation of CX3CR1 transcripts as measured by qPCR in wild-type (TREM2^{+/+}), R47H heterozygous (TREM2^{R47H/+}), and R47H homozygous (TREM2^{R47H}) macrophages at different time points in culture. All gene expression levels are normalized to wild-type control macrophages at Day 4 of culture.

[0061] **Figure 13G** depicts the differential regulation of FLT1 transcripts as measured by qPCR in wild-type (TREM2^{+/+}), heterozygous (TREM2^{+/-}), and knockout (TREM2^{-/-}) macrophages at different time points in culture. All gene expression levels are normalized to wild-type control macrophages at Day 4 of culture.

[0062] **Figure 13H** depicts the differential regulation of FLT1 transcripts as measured by qPCR in wild-type (TREM2^{+/+}), R47H heterozygous (TREM2^{R47H/+}), and R47H homozygous

(TREM2^{R47H}) macrophages at different time points in culture. All gene expression levels are normalized to wild-type control macrophages at Day 4 of culture.

[0063] **Figures 13I and 13J** depict the differential regulation of *Clqa* transcripts as measured by qPCR in wild-type (TREM2^{+/+}), R47H heterozygous (TREM2^{R47H/+}), and R47H homozygous (TREM2^{R47H/H}) macrophages at different time points in culture. All gene expression levels are normalized to wild-type control macrophages at Day 4 of culture.

[0064] **Figures 13K and 13L** depict the differential regulation of *Ccl5* transcripts as measured by qPCR in wild-type (TREM2^{+/+}), R47H heterozygous (TREM2^{R47H/+} and TREM2^{+/-}), and R47H homozygous (TREM2^{R47H/H} and TREM2^{-/-}) macrophages at different time points in culture. All gene expression levels are normalized to wild-type control macrophages at Day 4 of culture.

[0065] **Figures 13M and 13N** depict the differential regulation of *Ccl22* transcripts as measured by qPCR in wild-type (TREM2^{+/+}), R47H heterozygous (TREM2^{R47H/+} and TREM2^{+/-}), and R47H homozygous (TREM2^{R47H/H} and TREM2^{-/-}) macrophages at different time points in culture. All gene expression levels are normalized to wild-type control macrophages at Day 4 of culture.

[0066] **Figures 13O and 13P** depict the differential regulation of *C3* transcripts as measured by qPCR in wild-type (TREM2^{+/+}), R47H heterozygous (TREM2^{R47H/+} and TREM2^{+/-}), and R47H homozygous (TREM2^{R47H/H} and TREM2^{-/-}) macrophages at different time points in culture. All gene expression levels are normalized to wild-type control macrophages at Day 4 of culture.

[0067] **Figure 14A** is a graph depicting percent cell confluence over time in a culture compartment in a migration assay for wild-type (TREM2^{+/+}) and knockout (TREM2^{-/-}) BMDMs as measured by a real-time cell confluence assay. The TREM2 knockout macrophages exhibit a migration defect as compared to wild-type macrophages in this *in vitro* assay.

[0068] **Figure 14B** is a graph depicting percent cell confluence over time in a culture compartment in a migration assay for wild-type (TREM2^{+/+}) and TREM2^{R47H} BMDMs as measured by a real-time cell confluence assay. The TREM2^{R47H} macrophages exhibit a migration defect as compared to wild-type macrophages in this *in vitro* assay.

[0069] **Figure 15A** shows a reduction in secreted CCL2 protein from TREM2^{R47H} and TREM2^{-/-} macrophages as compared with wild-type (TREM2^{+/+}) macrophages as measured by ELISA.

[0070] **Figure 15B** depicts levels of secreted CCL2 protein as measured by ELISA from TREM2^{R47H} and wild-type TREM2^{+/+} macrophages treated with an anti-TREM2 agonist antibody or isotype control. Anti-TREM2 agonist antibody treatment restores levels of secreted CCL2 protein from TREM2^{R47H} macrophages.

[0071] **Figure 16A** shows the results of the pathway analysis of genes regulated by anti-TREM2 agonist antibody treatment in TREM2^{R47H} macrophages. The modulated genes include those involved in regulation of myeloid cell migration, proliferation, cell cycle and survival.

[0072] **Figure 16B** shows the RNA-Seq analysis comparing wildtype (TREM2^{+/+}), knockout (TREM2^{-/-}) and TREM2^{R47H} macrophages at day 7 under limiting conditions of CSF-1. Pathway analyses (WGCNA) identified 5 modules/gene networks that are differentially regulated in the knockout and TREM2^{R47H} macrophages compared to wild-type. The results indicate a role for TREM2 in cell cycle/proliferation and survival, immune response and migration and lipid and cholesterol homeostasis.

[0073] **Figure 16C** shows the differential regulation of UBE2C, MELK and MMP14 transcripts as measured by qPCR in wild-type (TREM2^{+/+}) and TREM2^{R47H} macrophages treated with an anti-TREM2 agonist antibody (Antibody 1) or isotype control. The data show that expression of the expression of the MMP14 enzyme is upregulated while the expression of the UBE2C and MELK enzymes is downregulated in the R47H macrophages, but the changes can be restored with treatment with the anti-TREM2 agonist antibody.

[0074] **Figure 17** shows that antibody treatment increases the expression of homeostatic microglial genes (P2ry12, Tmem119) in WT and R47H KI microglia, WT microglia alone and R47H KI microglia alone (A, B and C). Also antibody treatment reduces the expression pro-inflammatory chemokines and cytokines such as Ccl3, Ccl4, Ccl5, Il12b (D, E and F). All statistics are Wilcoxon rank scores. Expression is ln(counts+1).

[0075] **Figure 18** shows that the microglia infiltrate population has increased expression of myeloid and inflammatory genes and slightly lower expression of homeostatic microglia genes (A and B), and that the administration of Trem2 antibody decreased the pro-inflammatory chemokines and cytokines in the infiltrate microglia cells from WT and R47H KI mice, WT only mice and R47HKI only mice (C, D and E). All statistics are Wilcoxon rank scores. Expression is ln(counts+1) adjusted for umi count.

DETAILED DESCRIPTION

[0076] The present invention relates to isolated antigen binding proteins that specifically bind to TREM2, particularly human TREM2. In humans, the *TREM2* gene is located within a *TREM* gene cluster at chromosome 6p21.1. The *TREM* gene cluster encodes four TREM proteins (TREM1, TREM2, TREM4, and TREM5) as well as two TREM-like proteins (TLT-1 and TLT-2). The *TREM2* gene encodes a 230 amino acid protein consisting of an extracellular domain, a transmembrane region, and a short cytoplasmic tail (Paradowska-Gorycka *et al.*, Human Immunology, Vol. 74: 730-737, 2013). The extracellular domain contains a single type V Ig-super family domain, with three potential N-glycosylation sites. The wild-type human TREM2 amino acid sequence (NCBI Reference Sequence: NP_061838.1) is provided below as SEQ ID NO: 1.

```

1    MEPLRLILLILFVTELSGAHNTTVFQGVAGQSLQVSCPYDSMKHWGRRKAWCRQLGEKGPC    60
61    QRVVSTHNLWLLSFLRRWNGSTAITDDTLGGTLTITLRNLQPHDAGLYQCQSLHGSEADT
120
121    LRKVLVEVLADPLDHRDAGDLWFPGESESFEDAHVEHSISRSLLEGEIPFPPTSILLLLA
180
181    CIFLIKILAASALWAAAWHGQKPGTHPPSELDCGHDPGYQLQTLFGLRDT    230

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[0077] Amino acids 1 to 18 of the wild-type human TREM2 protein (SEQ ID NO: 1) is a signal peptide, which is generally removed from the mature protein. The mature human TREM2 protein comprises an extracellular domain at amino acids 19-174 of SEQ ID NO: 1, a transmembrane domain at amino acids 175-195 of SEQ ID NO: 1, and a cytoplasmic domain at amino acids 196-230 of SEQ ID NO: 1. The amino acid sequence of the extracellular domain (including the signal peptide) of human TREM2 is provided below as SEQ ID NO: 2.

```

1    MEPLRLILLILFVTELSGAHNTTVFQGVAGQSLQVSCPYDSMKHWGRRKAWCRQLGEKGPC
60
61    QRVVSTHNLWLLSFLRRWNGSTAITDDTLGGTLTITLRNLQPHDAGLYQCQSLHGSEADT
120
121    LRKVLVEVLADPLDHRDAGDLWFPGESESFEDAHVEHSISRSLLEGEIPFPPTS    174

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[0078] The term “human triggering receptor expressed on myeloid cells-2” or “human TREM2” can refer to a polypeptide of SEQ ID NO: 1, a polypeptide of SEQ ID NO: 2, polypeptides of SEQ ID NO: 1 or SEQ ID NO: 2 minus the signal peptide (amino acids 1-

18), allelic variants of human TREM2, or splice variants of human TREM2. In some embodiments, the term “human TREM2” includes naturally occurring variants of TREM2, such as mutations R47H, Q33X (X is a stop codon), Y38C, T66M, D87N, H157Y, R98W, and S116C.

[0079] Because the cytoplasmic domain of TREM2 lacks signaling capability, it must interact with other proteins to transduce TREM2-activating signals. One such protein is DNAX-activating protein of 12 kDa (DAP12). DAP12 is also known as killer cell activating receptor-associated protein (KARAP) and tyrosine kinases binding protein (TYROBP). DAP12 is a type I transmembrane adaptor protein that comprises an ITAM motif in its cytoplasmic domain. The ITAM motif mediates signal propagation by activation of the ZAP70 and Syk tyrosine kinases, which in turn activate several downstream signaling cascades, including PI3K, PKC, ERK, and elevation of intracellular calcium (Colonna, *Nature Reviews Immunology*, Vol. 3: 445-453, 2003; Ulrich and Holtzman, *ACS Chem. Neurosci.*, Vol. 7: 420-427, 2016). DAP12 and TREM2 associate through their transmembrane domains; a charged lysine residue within the transmembrane domain of TREM2 interacts with a charged aspartic acid residue within the transmembrane domain of DAP12.

[0080] Human DAP12 is encoded by the *TYROBP* gene located on chromosome 19q13.1. The human protein is 113 amino acids in length and comprises a leader sequence (amino acids 1-27 of SEQ ID NO: 3), a short extracellular domain (amino acids 28-41 of SEQ ID NO: 3), a transmembrane domain (amino acids 42-65 of SEQ ID NO: 3) and a cytoplasmic domain (amino acids 66-113 of SEQ ID NO: 3) (Paradowska-Gorycka *et al.*, *Human Immunology*, Vol. 74: 730-737, 2013). DAP12 forms a homodimer through two cysteine residues in the short extracellular domain. The wild-type human DAP12 amino acid sequence (NCBI Reference Sequence: NP_003323.1) is provided below as SEQ ID NO: 3.

```

1      MGGLEPCSRLLLPLLLAVSGLRPVQAQAQSDCSCSTVSPGVLGIVMGDLVLTVLIALA
60
61      VYFLGRLVPRGRGAEEAATRKQRITETESPYQELQGQRSDVYSDLNTQRPYYK   113

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[0081] The term “human DAP12” can refer to a polypeptide of SEQ ID NO: 3, a polypeptide of SEQ ID NO: 3 minus the leader peptide (amino acids 1-27), allelic variants of human DAP12, or splice variants of human DAP12.

[0082] In some embodiments, the present invention provides isolated antigen binding proteins that specifically bind to human TREM2. As used herein, the term “antigen binding protein” refers to a protein that specifically binds to one or more target antigens. An antigen binding protein typically comprises an antigen-binding fragment that specifically binds to an antigen and, optionally, a scaffold or framework portion that allows the antigen-binding fragment to adopt a conformation that promotes binding of the antigen binding protein to the antigen. An “antigen binding fragment,” used interchangeably herein with “binding fragment” or “fragment,” is a portion of an antibody that lacks at least some of the amino acids present in a full-length heavy chain and/or light chain, but which is still capable of specifically binding to an antigen. An antigen-binding fragment includes, but is not limited to, a single-chain variable fragment (scFv), a nanobody (e.g. VH domain of camelid heavy chain antibodies; VHH fragment, *see* Cortez-Retamozo *et al.*, Cancer Research, Vol. 64:2853-57, 2004), a Fab fragment, a Fab' fragment, a F(ab')₂ fragment, a Fv fragment, a Fd fragment, and a complementarity determining region (CDR) fragment, and can be derived from any mammalian source, such as human, mouse, rat, rabbit, or camelid. Antigen-binding fragments may compete for binding of a target antigen with an intact antibody and the fragments may be produced by the modification of intact antibodies (e.g. enzymatic or chemical cleavage) or synthesized *de novo* using recombinant DNA technologies or peptide synthesis. In some embodiments, the antigen-binding fragment comprises at least one CDR from an antibody that binds to the antigen, for example, the heavy chain CDR3 from an antibody that binds to the antigen. In other embodiments, the antigen-binding fragment comprises all three CDRs from the heavy chain of an antibody that binds to the antigen or all three CDRs from the light chain of an antibody that binds to the antigen. In still other embodiments, the antigen-binding fragment comprises all six CDRs from an antibody that binds to the antigen (three from the heavy chain and three from the light chain). In certain embodiments, an antigen binding protein is an antibody or binding fragment thereof.

[0083] An antigen binding protein can also include a protein comprising one or more antigen-binding fragments incorporated into a single polypeptide chain or into multiple polypeptide chains. For instance, antigen binding proteins can include, but are not limited to, a diabody (*see, e.g.*, EP 404,097; WO 93/11161; and Hollinger *et al.*, Proc. Natl. Acad. Sci. USA, Vol. 90:6444-6448, 1993); an intrabody; a domain antibody (single VL or VH domain or two or more VH domains joined by a peptide linker; *see* Ward *et al.*, Nature, Vol. 341:544-546, 1989); a maxibody (2 scFvs fused to Fc region, *see* Fredericks *et al.*, Protein

Engineering, Design & Selection, Vol. 17:95-106, 2004 and Powers *et al.*, Journal of Immunological Methods, Vol. 251:123-135, 2001); a triabody; a tetrabody; a minibody (scFv fused to CH3 domain; *see* Olafsen *et al.*, Protein Eng Des Sel., Vol. 17:315-23, 2004); a peptibody (one or more peptides attached to an Fc region, *see* WO 00/24782); a linear antibody (a pair of tandem Fd segments (VH-CH1-VH-CH1) which, together with complementary light chain polypeptides, form a pair of antigen binding regions, *see* Zapata *et al.*, Protein Eng., Vol. 8:1057-1062, 1995); a small modular immunopharmaceutical (*see* U.S. Patent Publication No. 20030133939); and immunoglobulin fusion proteins (e.g. IgG-scFv, IgG-Fab, 2scFv-IgG, 4scFv-IgG, VH-IgG, IgG-VH, and Fab-scFv-Fc; *see, e.g.*, Spiess *et al.*, Mol. Immunol., Vol. 67(2 Pt A):95-106, 2015).

[0084] The term “isolated molecule” (where the molecule is, for example, a polypeptide, a polynucleotide, antigen binding protein or an antibody) is a molecule that by virtue of its origin or source of derivation (1) is not associated with naturally associated components that accompany it in its native state, (2) is substantially free of other molecules from the same species (3) is expressed by a cell from a different species, or (4) does not occur in nature. Thus, a molecule that is chemically synthesized, or expressed in a cellular system different from the cell from which it naturally originates, will be “isolated” from its naturally associated components. A molecule also may be rendered substantially free of naturally associated components by isolation, using purification techniques well known in the art. Molecule purity or homogeneity may be assayed by a number of means well known in the art. For example, the purity of a polypeptide sample may be assayed using polyacrylamide gel electrophoresis and staining of the gel to visualize the polypeptide using techniques well known in the art. For certain purposes, higher resolution may be provided by using HPLC or other means well known in the art for purification.

[0085] In certain embodiments of the invention, the antigen binding proteins specifically bind to human TREM2. An antigen binding protein “specifically binds” to a target antigen when it has a significantly higher binding affinity for, and consequently is capable of distinguishing, that antigen compared to its affinity for other unrelated proteins, under similar binding assay conditions. Antigen binding proteins that specifically bind an antigen may have an equilibrium dissociation constant (K_D) $\leq 1 \times 10^{-6}$ M. The antigen binding protein specifically binds antigen with “high affinity” when the K_D is $\leq 1 \times 10^{-8}$ M. In one embodiment, the antigen binding proteins of the invention bind to human TREM2 with a K_D of $\leq 5 \times 10^{-7}$ M. In another embodiment, the antigen binding proteins of the invention bind to human TREM2

with a K_D of $\leq 1 \times 10^{-7}$ M. In yet another embodiment, the antigen binding proteins of the invention bind to human TREM2 with a K_D of $\leq 5 \times 10^{-8}$ M. In another embodiment, the antigen binding proteins of the invention bind to human TREM2 with a K_D of $\leq 1 \times 10^{-8}$ M. In certain embodiments, the antigen binding proteins of the invention bind to human TREM2 with a K_D of $\leq 5 \times 10^{-9}$ M. In other embodiments, the antigen binding proteins of the invention bind to human TREM2 with a K_D of $\leq 1 \times 10^{-9}$ M. In one particular embodiment, the antigen binding proteins of the invention bind to human TREM2 with a K_D of $\leq 5 \times 10^{-10}$ M. In another particular embodiment, the antigen binding proteins of the invention bind to human TREM2 with a K_D of $\leq 1 \times 10^{-10}$ M.

[0086] Affinity is determined using a variety of techniques, an example of which is an affinity ELISA assay. In various embodiments, affinity is determined by a surface plasmon resonance assay (e.g., BIAcore®-based assay). Using this methodology, the association rate constant (k_a in $M^{-1}s^{-1}$) and the dissociation rate constant (k_d in s^{-1}) can be measured. The equilibrium dissociation constant (K_D in M) can then be calculated from the ratio of the kinetic rate constants (k_d/k_a). In some embodiments, affinity is determined by a kinetic method, such as a Kinetic Exclusion Assay (KinExA) as described in Rathanaswami *et al.* Analytical Biochemistry, Vol. 373:52-60, 2008. Using a KinExA assay, the equilibrium dissociation constant (K_D in M) and the association rate constant (k_a in $M^{-1}s^{-1}$) can be measured. The dissociation rate constant (k_d in s^{-1}) can be calculated from these values ($K_D \times k_a$). In other embodiments, affinity is determined by a bio-layer interferometry method, such as that described in Kumaraswamy *et al.*, Methods Mol. Biol., Vol. 1278:165-82, 2015 and employed in Octet® systems (Pall ForteBio). The kinetic (k_a and k_d) and affinity (K_D) constants can be calculated in real-time using the bio-layer interferometry method. In some embodiments, the antigen binding proteins described herein exhibit desirable characteristics such as binding avidity as measured by k_d (dissociation rate constant) for human TREM2 of about 10^{-2} , 10^{-3} , 10^{-4} , 10^{-5} , 10^{-6} s^{-1} or lower (lower values indicating higher binding avidity), and/or binding affinity as measured by K_D (equilibrium dissociation constant) for human TREM2 of about 10^{-8} , 10^{-9} , 10^{-10} , 10^{-11} M or lower (lower values indicating higher binding affinity).

[0087] In certain embodiments, the antigen binding proteins of the invention specifically bind to human TREM2 with a K_D from about 1 pM to about 100 nM as measured by bio-layer interferometry at 25° C. For instance, in some embodiments, the antigen binding proteins of the invention specifically bind to human TREM2 with a K_D less than 100 nM as

measured by bio-layer interferometry at 25° C. In other embodiments, the antigen binding proteins of the invention specifically bind to human TREM2 with a K_D less than 50 nM as measured by bio-layer interferometry at 25° C. In yet other embodiments, the antigen binding proteins of the invention specifically bind to human TREM2 with a K_D less than 25 nM as measured by bio-layer interferometry at 25° C. In one particular embodiment, the antigen binding proteins of the invention specifically bind to human TREM2 with a K_D less than 10 nM as measured by bio-layer interferometry at 25° C. In another particular embodiment, the antigen binding proteins of the invention specifically bind to human TREM2 with a K_D less than 5 nM as measured by bio-layer interferometry at 25° C. In another particular embodiment, the antigen binding proteins of the invention specifically bind to human TREM2 with a K_D less than 1 nM as measured by bio-layer interferometry at 25° C.

[0088] The antigen binding proteins of the invention may, in some embodiments, bind to a particular region or epitope of human TREM2. As used herein, an “epitope” refers to any determinant capable of being specifically bound by an antigen binding protein, such as an antibody or fragment thereof. An epitope is a region of an antigen that is bound by, or interacts with, an antigen binding protein that targets that antigen, and when the antigen is a protein, includes specific amino acids that directly contact, or interact with, the antigen binding protein. An epitope can be formed both by contiguous amino acids or non-contiguous amino acids juxtaposed by tertiary folding of a protein. A “linear epitope” is an epitope where an amino acid primary sequence comprises the recognized epitope. A linear epitope typically includes at least 3 or 4 amino acids, and more usually, at least 5, at least 6, or at least 7 amino acids, for example, about 8 to about 10 amino acids in a unique sequence. A “conformational epitope”, in contrast to a linear epitope, is a group of discontinuous amino acids (e.g., in a polypeptide, amino acid residues that are not contiguous in the polypeptide’s primary sequence but that, in the context of the polypeptide’s tertiary and quaternary structure, are near enough to each other to be bound by an antigen binding protein). Epitope determinants can include chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl or sulfonyl groups, and can have specific three dimensional structural characteristics, and/or specific charge characteristics. Generally, antigen binding proteins specific for a particular target molecule will preferentially recognize an epitope on the target molecule in a complex mixture of proteins and/or macromolecules. In some embodiments, the antigen binding proteins bind to human TREM2 at an epitope within the extracellular domain of human TREM2 (SEQ ID NO: 2). In related embodiments, the

antigen binding proteins bind to human TREM2 at an epitope within amino acids 19-174 of SEQ ID NO: 1. In certain embodiments, the antigen binding proteins bind to human TREM2 at an epitope within amino acids 23-128 of SEQ ID NO: 1.

[0089] In certain embodiments, the antigen binding proteins of the invention do not specifically bind to human TREM1. Like TREM2, TREM1 is a transmembrane glycoprotein that is expressed on myeloid cells and signals through DAP12. Activation of TREM1 signaling results in inflammatory effects, such as pro-inflammatory cytokine production, degranulation of neutrophils, and phagocytosis (Arts *et al.*, Journal of Leukocyte Biology, Vol. 93: 209-215, 2013). As discussed above, TREM1 is encoded by the *TREM1* gene, which is located in the *TREM* gene cluster along with the *TREM2* gene at chromosome 6p21.1. The wild-type human TREM1 amino acid sequence (NCBI Reference Sequence: NP_061113.1) is provided below as SEQ ID NO: 4.

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1      MRKTRLWGLLWMLFVSELRAATKLTEEKYELKEGQTLDVKCDYTLKFASSQKAWQIIRD
60
61      GEMPKTLACTERPSKNSHPVQVGRIILEDYHDHGLLRVRMVNLQVEDSGLYQCVIYQPPK
120
121     EPHMLFDRIRLVVTKGFSGTPGSNENSTQNVYKIPPTTTKALCPLYTSPRTVTQAPPKST
180
181     ADVSTPDSEINLTNVTDIIRVPVFNIVILLAGGFSLKSLVFSVLEFAVTLRSFVP    234

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[0090] The term “human TREM1” can refer to a polypeptide of SEQ ID NO: 4, a polypeptide of SEQ ID NO: 4 minus the signal peptide (amino acids 1-20), allelic variants of human TREM1, or splice variants of human TREM1. An antigen binding protein of the invention “does not specifically bind” to human TREM1 if it has an equivalent or lower binding affinity for human TREM1 as it does for an unrelated human antigen protein. Antigen binding proteins that do not specifically bind to human TREM1 may have a K_D for human TREM1 $\geq 1 \times 10^{-5}$ M, $\geq 1 \times 10^{-4}$ M, or $\geq 1 \times 10^{-3}$ M as determined by any of the methods for measuring affinity as described herein. An antigen binding protein of the invention may be considered to not specifically bind human TREM1 if the antigen binding protein has equivalent or lower binding to human TREM1 as compared to the binding to human TREM1 of an isotype control antibody as measured by any method known in the art, such as the FACS binding method described in Example 2.

[0091] In certain embodiments, the antigen binding proteins of the invention are agonist antigen binding proteins. An “agonist antigen binding protein” or “activating antigen binding protein” is an antigen binding protein (e.g. an antibody) that binds to and induces or increases one or more TREM2-mediated functions or activities. TREM2-mediated functions or activities include, but are not limited to, DAP12 phosphorylation (e.g. tyrosine phosphorylation within the ITAM motif within the DAP12 cytoplasmic domain); Syk phosphorylation; Src phosphorylation/activation; activation/phosphorylation of extracellular regulated kinase (ERK1/2); translocation of activated phosphatidylinositol 3-kinase (PI3K) to the membrane; activation of protein kinase B (PKB, also known as Akt); activation of NF- κ B and NF- κ B-mediated transcription; activation of nuclear factor of activated T-cells (NFAT)-mediated transcription; activation of protein kinase C (PKC); elevation of intracellular inositol (1,4,5)-triphosphate (IP3); elevation of intracellular calcium levels; increase in survival or proliferation of myeloid cells, such as macrophages, microglia, and dendritic cells; reduction of apoptosis of myeloid cells, such as macrophages, microglia, and dendritic cells; increase in CCL2 protein expression in macrophages; reduction of inflammatory cytokine (e.g. TNF- α , IL-6, IL-10, IL-12p70, and IFN- γ) production from myeloid cells (e.g. macrophages), and increase in phagocytosis by macrophages and microglia of necrotic and/or apoptotic cells (e.g. neuronal cells), cellular debris, and misfolded peptides.

[0092] The agonist TREM2 antigen binding proteins of the invention are capable of inducing or activating TREM2-mediated functions in the absence of aggregation, clustering, and/or Fc-mediated cross-linking of the antigen binding proteins. Accordingly, *in vitro*, the agonist activity of the antigen binding proteins can be detected with soluble (i.e. not bound to a solid support), monomeric, bivalent forms of the antigen binding proteins or antibodies. *In vivo*, the agonist activity of the antigen binding proteins of the invention can occur in the absence of the antigen binding proteins binding to receptors (e.g. Fc receptors) on adjacent cells to cluster or aggregate the antigen binding protein. Thus, in some embodiments, the agonist activity of the antigen binding proteins described herein is independent of the ability of the antigen binding proteins to bind to or interact with Fc receptors. In embodiments in which the antigen binding proteins comprise an Fc region (e.g. antibodies), the antigen binding proteins retain TREM2 agonist activity without binding or interacting with an Fc γ receptor, such as the Fc γ RIIB receptor. The cross-linking independent nature of the agonist antigen binding proteins of the invention is advantageous for therapeutic uses of the antigen binding proteins

because the agonist activity of the antigen binding proteins will not vary with the Fc γ receptor expression or accessibility at the therapeutic site of action.

[0093] The dependence of TREM2 agonist activity on cross-linking, aggregation, and/or clustering of the antigen binding proteins can be assessed by measuring activation or induction of any of the TREM2-mediated functions described herein in the absence of a cross-linking agent. A cross-linking agent can be any agent that interacts with antigen binding proteins at a site other than the antigen-binding site to cluster two or more antigen binding proteins together. In embodiments in which the antigen-binding protein comprises an Fc region (e.g. an antibody), a cross-linking agent can be a protein that binds to or interacts with the Fc region, such as protein A, protein G, an anti-Fc antibody, or Fc γ receptor.

[0094] In some embodiments, a TREM2 agonist antigen binding protein of the invention increases levels of phosphorylated Syk (pSyk) in cells expressing a TREM2 protein (e.g. a human TREM2 protein) relative to pSyk levels in the absence of the antigen binding protein or relative to pSyk levels in the presence of a control. The cells can be cells of a myeloid lineage including, but not limited to, monocytes, macrophages, microglial cells, dendritic cells, osteoclasts, neutrophils, basophils, eosinophils, megakaryocytes, and platelets. In certain embodiments, the TREM2 agonist antigen binding proteins increase pSyk levels with an EC₅₀ less than about 100 nM, less than about 80 nM, less than about 60 nM, less than about 50 nM, less than about 40 nM, less than about 30 nM, less than about 20 nM, less than about 10 nM, less than about 5 nM, less than about 1 nM, less than about 500 pM, less than about 300 pM, or less than about 100 pM. In some embodiments, the TREM2 agonist antigen binding proteins increase pSyk levels with an EC₅₀ from about 1 pM to about 100 nM, from about 10 pM to about 50 nM, from about 50 pM to about 5 nM, from about 100 pM to about 1 nM, or from about 150 pM to about 500 pM. An "EC₅₀" or "half maximal effective concentration" is a measure of potency of the antigen binding protein and refers to the concentration of antigen binding protein required to induce a response halfway between baseline and maximal response after a particular exposure period. The EC₅₀ of any particular agonist can be determined by constructing a dose-response curve and examining the effect of different concentrations of the agonist in inducing activity in a particular functional assay (e.g. pSyk levels). The EC₅₀ is the concentration of the agonist at which 50% of its maximal effect is observed. Increases in intracellular pSyk levels induced by the TREM2 agonist antigen binding proteins of the invention can be assessed by various methods, such as the cell-based assays described in Examples 2 and 6. For instance, cells expressing TREM2 (e.g.

human TREM2) are contacted with one or more concentrations of an agonist antigen binding protein, the cells are lysed, and pSyk levels in the cell lysates are assessed, for example by Western blot, FRET-based assay or chemiluminescent assay (e.g. AlphaLISA-based assay). The cells in the cell-based assay may be cells, such as HEK293T cells or CHO cells, which recombinantly express TREM2 (e.g. human TREM2). Alternatively, the cells in the cell-based assay are cells that natively express TREM2 (e.g. human TREM2), such as THP-1 cells, macrophage, microglial cells, or dendritic cells.

[0095] In certain embodiments, the potency of the TREM2 agonist antigen binding proteins for inducing or increasing pSyk levels in a cell expressing TREM2 (e.g. human TREM2) is retained in the absence of a cross-linking agent. For instance, in some embodiments, the TREM2 agonist antigen binding proteins of the invention increase pSyk levels with an EC₅₀ from about 1 pM to about 100 nM, from about 10 pM to about 50 nM, from about 50 pM to about 5 nM, from about 100 pM to about 1 nM, or from about 150 pM to about 500 pM in the absence of a cross-linking agent as measured by a cell-based pSyk assay. In one embodiment, the TREM2 agonist antigen binding protein increases pSyk levels with an EC₅₀ less than 5 nM in the absence of a cross-linking agent as measured by a cell-based pSyk assay. In another embodiment, the TREM2 agonist antigen binding protein increases pSyk levels with an EC₅₀ less than 1 nM in the absence of a cross-linking agent as measured by a cell-based pSyk assay. In another embodiment, the TREM2 agonist antigen binding protein increases pSyk levels with an EC₅₀ less than 500 pM in the absence of a cross-linking agent as measured by a cell-based pSyk assay. In still another embodiment, the TREM2 agonist antigen binding protein increases pSyk levels with an EC₅₀ less than 300 pM in the absence of a cross-linking agent as measured by a cell-based pSyk assay. In yet another embodiment, the TREM2 agonist antigen binding protein increases pSyk levels with an EC₅₀ less than 100 pM in the absence of a cross-linking agent as measured by a cell-based pSyk assay.

[0096] The TREM2 agonist antigen binding proteins of the invention may comprise one or more complementarity determining regions (CDRs) from the light and heavy chain variable regions of antibodies that specifically bind to human TREM2 as described herein. The term “CDR” refers to the complementarity determining region (also termed “minimal recognition units” or “hypervariable region”) within antibody variable sequences. There are three heavy chain variable region CDRs (CDRH1, CDRH2 and CDRH3) and three light chain variable region CDRs (CDRL1, CDRL2 and CDRL3). The term “CDR region” as used herein refers to a group of three CDRs that occur in a single variable region (i.e. the three light chain

CDRs or the three heavy chain CDRs). The CDRs in each of the two chains typically are aligned by the framework regions (FRs) to form a structure that binds specifically with a specific epitope or domain on the target protein (e.g., human TREM2). From N-terminus to C-terminus, naturally-occurring light and heavy chain variable regions both typically conform with the following order of these elements: FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. A numbering system has been devised for assigning numbers to amino acids that occupy positions in each of these domains. This numbering system is defined in Kabat Sequences of Proteins of Immunological Interest (1987 and 1991, NIH, Bethesda, MD), or Chothia & Lesk, 1987, *J. Mol. Biol.* 196:901-917; Chothia *et al.*, 1989, *Nature* 342:878-883. Complementarity determining regions (CDRs) and framework regions (FR) of a given antibody may be identified using this system. Other numbering systems for the amino acids in immunoglobulin chains include IMGT® (the international ImMunoGeneTics information system; Lefranc *et al.*, *Dev. Comp. Immunol.* 29:185-203; 2005) and AHO (Honegger and Pluckthun, *J. Mol. Biol.* 309(3):657-670; 2001). One or more CDRs may be incorporated into a molecule either covalently or noncovalently to make it an antigen binding protein.

[0097] In some embodiments, an antigen binding protein of the invention may incorporate the CDR(s) as part of a larger polypeptide chain, may covalently link the CDR(s) to another polypeptide chain, or may incorporate the CDR(s) noncovalently. The antigen binding proteins may comprise at least one of the CDRs described herein incorporated into a biocompatible framework structure. In one example, the biocompatible framework structure comprises a polypeptide or portion thereof that is sufficient to form a conformationally stable structural support, or framework, or scaffold, which is able to display one or more sequences of amino acids that bind to an antigen (e.g., CDRs, a variable region, etc.) in a localized surface region. Such structures can be a naturally occurring polypeptide or polypeptide “fold” (a structural motif), or can have one or more modifications, such as additions, deletions or substitutions of amino acids, relative to a naturally occurring polypeptide or fold. These scaffolds can be derived from a polypeptide of any species (or of more than one species), such as a human, other mammal, other vertebrate, invertebrate, plant, bacteria or virus.

[0098] In certain embodiments, the TREM2 agonist antigen binding proteins of the invention comprise at least one light chain variable region comprising a CDRL1, CDRL2, and CDRL3, and at least one heavy chain variable region comprising a CDRH1, CDRH2, and CDRH3 from an anti-TREM2 agonist antibody described herein. Light chain and heavy chain variable

regions and associated CDRs of exemplary human anti-TREM2 antibodies are set forth below in Tables 1A and 1B, respectively.

Table 1A. Exemplary Anti-Human TREM2 Antibody Light Chain Variable Region Amino Acid Sequences

Ab ID.	VL Group	VL Amino Acid Sequence	CDRL1	CDRL2	CDRL3
12G10	LV-01	QAVPTQPSSLSASPGV LASLTCTLRSGINVT YRIYWYQQKPGSPQ YLLRYKSDSDKQQGS GVPSRFSGSKDASANA GILLISGLQSEDEADYY CMIWYSSAVVFGGGT KLTVL (SEQ ID NO: 46)	TLRSGINVTYRIY (SEQ ID NO: 5)	YKSDSDKQQGS (SEQ ID NO: 19)	MIWYSSAVV (SEQ ID NO: 31)
26A10	LV-02	SYELTQPPSVSVSPGQ TASITCSGDKLGDKYV CWYQQKPGQSPVLVI YQDSKRPSGIPERFSGS NSGNTATLTISGTQAM DEADYYCQAWDSNTV VFGGGTKLTVL (SEQ ID NO: 47)	SGDKLGDKYVC (SEQ ID NO: 6)	QDSKRPS (SEQ ID NO: 20)	QAWDSNTVV (SEQ ID NO: 32)
26C10	LV-03	SFELTQPPSVSVSPGQT ASITCSGDKLGDKYVC WYQQKPGQSPMLVIY QDTKRPSGIPERFSGSN SGNTATLTISGTQAMD EADYYCQAWDSSTVV FVGGGTKLTVL (SEQ ID NO: 48)	SGDKLGDKYVC (SEQ ID NO: 6)	QDTKRPS (SEQ ID NO: 21)	QAWDSSTVV (SEQ ID NO: 33)
26F2	LV-04	SYELTQPPSVSVSPGQ TASITCSGDKLGDKYV CWYQQKPGQSPVLVIF QDSKRPSGIPERFSGSN SGNTATLTISGTQAMD EADYYCQAWDSSTVV FVGGGTKLTVL (SEQ ID NO: 49)	SGDKLGDKYVC (SEQ ID NO: 6)	QDSKRPS (SEQ ID NO: 20)	QAWDSSTVV (SEQ ID NO: 33)
33B12	LV-05	SYELTQPPSVSVSPGQ TASITCSGDKLGDKYV CWYQQKPGQSPVLVI YQDSKRPSGIPERFSGS NSGNTATLTISGTQAM DEADYYCQAWDSSTV VFGGGTKLTVL (SEQ ID NO: 50)	SGDKLGDKYVC (SEQ ID NO: 6)	QDSKRPS (SEQ ID NO: 20)	QAWDSSTVV (SEQ ID NO: 33)
24C12	LV-06	GIVMTQSPDSLAVSLG ERATINCKSSRSVLYSS NNKNYLAWYQQKPG QPPKVLIIWASTRESG VPDRFSGSGSGTDFTL TISSLQAEDVAVYNCO QYYITPITFGQGRLEI K (SEQ ID NO: 51)	KSSRSVLYSSNNKNYLA (SEQ ID NO: 7)	WASTRES (SEQ ID NO: 22)	QYYITPIT (SEQ ID NO: 34)

Ab ID.	VL Group	VL Amino Acid Sequence	CDRL1	CDRL2	CDRL3
24G6	LV-07	DIVMTQSPDSLAVSLG ERATINCKSSQSVLYSS NNKHFLAWYQQKPGQ PPKLLIYWASTRESGV PDRFSGSGSGTDFTLTI SSLQAEDVAFYYCQQ YYSTPLTFGGGKVEI K (SEQ ID NO: 52)	KSSQSVLYSSNNKHFLA (SEQ ID NO: 8)	WASTRES (SEQ ID NO: 22)	QQYYSTPLT (SEQ ID NO: 35)
24A10	LV-08	DIVMTQSPDSLAVSLG ERATITCKSSHNVLYS SNNKNYLAWYQQKPG QPPKLLIYWASTRESG VPDRFSGSGSGTDFTL TISSLQAEDVAVYYCH QYYSTPCSFQGQTKLE IK (SEQ ID NO: 53)	KSSHNVLSSNNKNYLA (SEQ ID NO: 9)	WASTRES (SEQ ID NO: 22)	HQYYSTPCS (SEQ ID NO: 36)
10E3	LV-09	EIVMTQSPATLSVSPG ERATLSCRASQSVSSN LAWFQQKPGQAPRLLI YGASTRATGIPARFSV SGSGTEFTLTISLQSE DFAFYCYCLQDNNWPP TFGPGTKVDIK (SEQ ID NO: 54)	RASQSVSSNLA (SEQ ID NO: 10)	GASTRAT (SEQ ID NO: 23)	LQDNNWPPT (SEQ ID NO: 37)
13E7 14C12	LV-10	EIVMTQSPATLSVSPG ERATLSCRASQSVSSN LAWFQQKPGQAPRLLI YGASTRATGIPARFSV SGSGTEFTLTISLQSE DFAVYYCYCLQDNNWPP TFGPGTKVDIK (SEQ ID NO: 55)	RASQSVSSNLA (SEQ ID NO: 10)	GASTRAT (SEQ ID NO: 23)	LQDNNWPPT (SEQ ID NO: 37)
25F12	LV-11	EKVMQSPATLSVSPG ERATLSCRASQSVNNN LAWYQQKPGQAPRLI IYGASTRATGIPARFSG SGSGTEFTLTISLQSE DFAVYYCQQYNNWPR TFGQGTKVEIK (SEQ ID NO: 56)	RASQSVNNNLA (SEQ ID NO: 11)	GASTRAT (SEQ ID NO: 23)	QQYNNWPRT (SEQ ID NO: 38)
32E3	LV-12	EFVLTQSPGTLSPGE RATLSCRASQHSNYL AWYQQKPGQAPRLLI YSASSRATGIPDRFSGS GSGTDFTLTISRLEPED FAVYYCQQFDSSPITF GRGTRLDIK (SEQ ID NO: 57)	RASQHSNNYLA (SEQ ID NO: 12)	SASSRAT (SEQ ID NO: 24)	QQFDSSPIT (SEQ ID NO: 39)
24F4	LV-13	EIVLTQSPGTLSPGE RATLSCRASQSVSSY LAWYQQKPGQAPRLI IYGASSRATGIPDRFSG SGSGTDFTLTISRLEPE DFALYYCQQYDTSPFT FGPGTKVDIK (SEQ ID NO: 58)	RASQSVSSSYLA (SEQ ID NO: 13)	GASSRAT (SEQ ID NO: 25)	QQYDTSPFT (SEQ ID NO: 40)

Ab ID.	VL Group	VL Amino Acid Sequence	CDRL1	CDRL2	CDRL3
16B8	LV-14	DIQMTQSPSSVSASVG DRVTVTCRASQDINS WLAWYQQKPGKAPK LLIYAASSLQGTGVP SRFSGSGSGTDFTLTI SSLPEDFATYSCQQSN SPITFGQGTRLEIK (SEQ ID NO: 59)	RASQDINSWLA (SEQ ID NO: 14)	AASSLQT (SEQ ID NO: 26)	QQSNSFPIT (SEQ ID NO: 41)
4C5	LV-15	DIQMTQSPSSVSASVG DRVITTCRASQGISNW LAWYQQKPGKAPKLL IYAASSLQVGVPLRFS GSGSGTDFTLTISSLP QPEDFATYYCQQADSF PRNFGQGTKLEIK (SEQ ID NO: 60)	RASQGISNWLA (SEQ ID NO: 15)	AASSLQV (SEQ ID NO: 27)	QQADSFPRN (SEQ ID NO: 42)
6E7	LV-16	DIQMTQSPSSVSASVG DRVITTCRASQGISSW LAWYQQKPGKAPKLL IYAASSLQNGVPSRFS GSGSGTDFTLTISSLP QPEDFATYFCQQADSF PRNFGQGTKLEIK (SEQ ID NO: 61)	RASQGISSWLA (SEQ ID NO: 16)	AASSLQN (SEQ ID NO: 28)	QQADSFPRN (SEQ ID NO: 43)
5E3	LV-17	DIQMTQSPSSLSASVG DRVITTCRASQGISNY LAWFQQKPGKAPKSLI YAASSLQSGVPSKFS GSGSGTDFTLTISSLP QPEDFATYYCQQYSTY PFTFGPGTKVDIK (SEQ ID NO: 62)	RASQGISNYLA (SEQ ID NO: 17)	AASSLQS (SEQ ID NO: 29)	QQYSTYPFT (SEQ ID NO: 44)
4G10	LV-18	DIQMTQSPSSLSASVG DRVITTCRASQGIRND LGWYQQKPGNAPKRL IYAASSLPSGVPSRFS GSGSGPEFTLTISSLP QPEDFATYYCLQHNSY PWTFGQGTVKVEIT (SEQ ID NO: 63)	RASQGIRNDLG (SEQ ID NO: 18)	AASSLPS (SEQ ID NO: 30)	LQHNSYPWT (SEQ ID NO: 45)

Table 1B. Exemplary Anti-Human TREM2 Antibody Heavy Chain Variable Region Amino Acid Sequences

Ab ID.	VH Group	VH Amino Acid Sequence	CDRH1	CDRH2	CDRH3
12G10 24C12	HV-01	EVQLLESQGGGLVQ PGGSLRLSCAASG FTFSSYAMSWVRQ APGKGLEWVSAIG GGGVSTYCADSV KGRFTISRDNSKN TLYLQMNSLRAED TAVYYCAKFYIAV AGSHFDYWGGQT LVTVSS (SEQ ID NO: 110)	SYAMS (SEQ ID NO: 77)	AIGGGGVSTYCADSVKG (SEQ ID NO: 87)	FYIAVAGSHFDY (SEQ ID NO: 95)

Ab ID.	VH Group	VH Amino Acid Sequence	CDRH1	CDRH2	CDRH3
26A10	HV-02	EVQLVESGGALVQ RGGSLRLSCAASR FTFSSFGMSWVRQ APGKGLEWVSYIS SSSFTIYYADSVKG RFTISRDNKNSF YLQMNSLRDEDT AVYYCAREGGLT MVRGVSSYGLDV WGQGTTTVTVSS (SEQ ID NO: 111)	SFGMS (SEQ ID NO: 78)	YISSSSFTIYYADSVKG (SEQ ID NO: 88)	EGGLTMVRGVSSYGLDV (SEQ ID NO: 96)
26C10	HV-03	EVQLVESGGALVQ PGGSLRLSCAASG FTFSSFGMSWVRQ APGKGLEWVSYIS SSSFTIYYADSVKG RFTISRDNKNSF YLQMNSLRDEDT AVYFCVREGGITM VRGVSSYGMDVW GQGTTTVTVSS (SEQ ID NO: 112)	SFGMS (SEQ ID NO: 78)	YISSSSFTIYYADSVKG (SEQ ID NO: 88)	EGGITMVRGVSSYGMVDV (SEQ ID NO: 97)
26F2	HV-04	EVQLVESGGALVQ PGGSLRLSCAASG FTFSSFGMSWVRQ APGKGLEWISYISS SSFTIYYADSVKG RFTISRDNKNSF YLQMNSLRDEDT AVYFCAREGGITM VRGVSSYGMDVW GQGTTTVTVSS (SEQ ID NO: 113)	SFGMS (SEQ ID NO: 78)	YISSSSFTIYYADSVKG (SEQ ID NO: 88)	EGGITMVRGVSSYGMVDV (SEQ ID NO: 97)
33B12	HV-05	EVQLVESGGALVQ PGGSLRLSCAASG FTFSSFGMSWVRQ APGKGLEWVSYIS KSSFTIYYADSVK GRFTISRDNKNS FYLMNSLRDEDT AVYYCAREGGLT MVRGVSSYGLDV WGQGTTTVTVSS (SEQ ID NO: 114)	SFGMS (SEQ ID NO: 78)	YISKSSFTIYYADSVKG (SEQ ID NO: 89)	EGGLTMVRGVSSYGLDV (SEQ ID NO: 96)
24G6	HV-06	EVQLLESGGGLVQ PGGSLRLSCAASG FTFSSYAMSWVRQ APGKGLEWVSAIS GSGGSTYYADSVK GRFTISRDNKNTL YLQMNSLRAEDT AVYYCAKAYTPM AFFDYWGQGTLLV TVSS (SEQ ID NO: 115)	SYAMS (SEQ ID NO: 77)	AISGSGGSTYYADSVKG (SEQ ID NO: 90)	AYTPMAFFDY (SEQ ID NO: 98)

Ab ID.	VH Group	VH Amino Acid Sequence	CDRH1	CDRH2	CDRH3
24A10	HV-07	EVQVLESGGGLVQ PGGSLRLSCAASG FTFSNYAMSWVR QAPGKGLEWVSAI SGSGGSTYYADSV KGRFTISRDNSKN TLYLQMNSLRAED TAVYYCAKGGWE LFYWGQGTLLTV SS (SEQ ID NO: 116)	NYAMS (SEQ ID NO: 79)	AISGSGGSTYYADSVKG (SEQ ID NO: 90)	GGWELFY (SEQ ID NO: 99)
10E3	HV-08	EVQLVQSGAEVK KPGESLMISCKGS GYSFTNYWIGWV RQMPGKGLEWMG IYPGDS DTRYSPS FQGQVTISADKSIS TAYLQWSSLKASD TAMYFCARRRQGI WGDALDIWGQGT LTVVSS (SEQ ID NO: 117)	NYWIG (SEQ ID NO: 80)	IYPGDS DTRYSPSFQG (SEQ ID NO: 91)	RRQGIWGDALDI (SEQ ID NO: 100)
13E7 14C12	HV-09	EVQLVQSGAEVK KPGESLMISCKGS GYSFTSYWIGWVR QMPGKGLEWMGII YPGDS DTRYSPSF QGQVTISADKSIST AYLQWSSLKASDT AMYFCARRRQGI WGDALDFWGQGT LTVVSS (SEQ ID NO: 118)	SYWIG (SEQ ID NO: 81)	IYPGDS DTRYSPSFQG (SEQ ID NO: 91)	RRQGIWGDALDF (SEQ ID NO: 101)
25F12	HV-10	QVQLQQWGAGLL KPSETLSLTCAVY GGSFSSYYWSWIR QPPGKGLEWIGEI NHSGNTNYPNPSLK SRVTISVDTSKNQF SLKLSSVTAADTA VYYCAREGYDIL TGYHDAFDIWDQ GTMVTVFS (SEQ ID NO: 119)	SYWWS (SEQ ID NO: 82)	EINHSGNTNYPNPSLKS (SEQ ID NO: 92)	EGYYDILTGYHDAFDI (SEQ ID NO: 102)
32E3	HV-11	EVQLVQSGAEVK KPGESLKISCKGSG YSFTSYWIGWVRQ MPGKGLEWMGIIY PGDS DTRYSPSFQ GQVTISADKSISTA YLQWSTLKASDT AIYYCARHDIIPAA PGAFDIWGQGT MTVSS (SEQ ID NO: 120)	SYWIG (SEQ ID NO: 81)	IYPGDS DTRYSPSFQG (SEQ ID NO: 91)	HDIIIPAAPGAFDI (SEQ ID NO: 103)

Ab ID.	VH Group	VH Amino Acid Sequence	CDRH1	CDRH2	CDRH3
24F4	HV-12	EVQLVQSGAEVK KPGESLKISCKGSG YTFTSYWIGWVR QMPGKGLEWMGII YPGDS DTRYSPSF QGQVTISVDKSSS TAYLQWSSLKASD TAIYYCTRQAIAV TGLGGFDPWGQG TLVTVSS (SEQ ID NO: 121)	SYWIG (SEQ ID NO: 81)	IYPGDS DTRYSPSFQG (SEQ ID NO: 91)	QAIAVTGLGGFDP (SEQ ID NO: 104)
16B8	HV-13	QVQLVQSGAEVK KPGASVKVSCCKAS GYTFTNYGISWVR QAPGQGLEWMG WISAYNGNTNYA QKLQGRVTMTTD TSTSTVYME LRSL RSDDTAVYYCAR RGYSYGSFDYWG QGTLVTVSS (SEQ ID NO: 122)	NYGIS (SEQ ID NO: 83)	WISAYNGNTNYA QKLQG (SEQ ID NO: 93)	RGYSYGSFDY (SEQ ID NO: 105)
4C5	HV-14	EVQLVQSGAEVK KPGESLKISCKGSG HSFTNYWIAWVR QMPGKGLEWMGII YPGDS DTRYSPSF QGQVTISADKSIST AYLQWSSLKASDT AVYFCARQRTFYY DSSGYFDYWGQG TLVTVSS (SEQ ID NO: 123)	NYWIA (SEQ ID NO: 84)	IYPGDS DTRYSPSFQG (SEQ ID NO: 91)	QRTFYYDSSGYFDY (SEQ ID NO: 106)
6E7	HV-15	EVQLVQSGAEVK KPGESLKISCKGSG YSFTSYWIAWVRQ MPGKGLEWMGII PGDS DTRYSPSFQ GQVTISADKSISTA YLQWSSLKASDTA MYFCARQRTFYY DSSDYFDYWGQG TLVTVSS (SEQ ID NO: 124)	SYWIA (SEQ ID NO: 85)	IYPGDS DTRYSPSFQG (SEQ ID NO: 91)	QRTFYYDSSDYFDY (SEQ ID NO: 107)
5E3	HV-16	QVQLVQSGAEVK KPGASVKVSCCKAS GYTFTGYIHWVR QAPGLGLEWMGW INPYSGGTSAQK FQGRVTMTRDTSI SSAYMELSRLRSD DTAVYYCARDGG YLALYGTDVWGQ GTTVTVSS (SEQ ID NO: 125)	GYIYH (SEQ ID NO: 86)	WINPYSGGTSAQKFQG (SEQ ID NO: 94)	DGGYLALYGTDV (SEQ ID NO: 108)

Ab ID.	VH Group	VH Amino Acid Sequence	CDRH1	CDRH2	CDRH3
4G10	HV-17	EVQLVQSGAEVK KPGESLKISCKGSG YSFPSYWIAWVRQ MPGKGLEWMGIHY PGDSDTRYSPSFQ GQVTISADKSISTA FLKWSSSLKASDTA MYFCARQGIEVTG TGGLDVWGQGGT VTVSS (SEQ ID NO: 126)	SYWIA (SEQ ID NO: 85)	IYPGDSDDTRYSPSFQ (SEQ ID NO: 91)	QGIEVTGTGGLDV (SEQ ID NO: 109)

[0099] The TREM2 agonist antigen binding proteins of the invention may comprise one or more of the CDRs presented in Table 1A (light chain CDRs; i.e. CDRLs) and Table 1B (heavy chain CDRs, i.e. CDRHs). For instance, in certain embodiments, the TREM2 agonist antigen binding proteins comprise one or more light chain CDRs selected from (i) a CDRL1 selected from SEQ ID NOs: 5 to 18, (ii) a CDRL2 selected from SEQ ID NOs: 19 to 30, and (iii) a CDRL3 selected from SEQ ID NOs: 31 to 45, and (iv) a CDRL of (i), (ii) and (iii) that contains one or more, e.g., one, two, three, four or more amino acid substitutions (e.g., conservative amino acid substitutions), deletions or insertions of no more than five, four, three, two, or one amino acids. In these and other embodiments, the TREM2 agonist antigen binding proteins comprise one or more heavy chain CDRs selected from (i) a CDRH1 selected from SEQ ID NOs: 77 to 86, (ii) a CDRH2 selected from SEQ ID NOs: 87 to 94, and (iii) a CDRH3 selected from SEQ ID NOs: 95 to 109, and (iv) a CDRH of (i), (ii) and (iii) that contains one or more, e.g., one, two, three, four or more amino acid substitutions (e.g., conservative amino acid substitutions), deletions or insertions of no more than five, four, three, two, or one amino acids.

[0100] In certain embodiments, the TREM2 agonist antigen binding proteins may comprise 1, 2, 3, 4, 5, or 6 variant forms of the CDRs listed in Tables 1A and 1B, each having at least 80%, 85%, 90% or 95% sequence identity to a CDR sequence listed in Tables 1A and 1B. In some embodiments, the TREM2 agonist antigen binding proteins include 1, 2, 3, 4, 5, or 6 of the CDRs listed in Tables 1A and 1B, each differing by no more than 1, 2, 3, 4 or 5 amino acids from the CDRs listed in these tables. In some embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a CDRL1 comprising a sequence selected from SEQ ID NOs: 5-18 or a variant thereof having one, two, three or four amino acid substitutions; a CDRL2 comprising a sequence selected from SEQ ID NOs: 19-30 or a variant thereof having one, two, three or four amino acid substitutions; a CDRL3 comprising

a sequence selected from SEQ ID NOs: 31-45 or a variant thereof having one, two, three or four amino acid substitutions; a CDRH1 comprising a sequence selected from SEQ ID NOs: 77-86 or a variant thereof having one, two, three or four amino acid substitutions; a CDRH2 comprising a sequence selected from SEQ ID NOs: 87-94 or a variant thereof having one, two, three or four amino acid substitutions; and a CDRH3 comprising a sequence selected from SEQ ID NOs: 95-109 or a variant thereof having one, two, three or four amino acid substitutions. In other embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a CDRL1 comprising a sequence selected from SEQ ID NOs: 5-18; a CDRL2 comprising a sequence selected from SEQ ID NOs: 19-30; a CDRL3 comprising a sequence selected from SEQ ID NOs: 31-45; a CDRH1 comprising a sequence selected from SEQ ID NOs: 77-86; a CDRH2 comprising a sequence selected from SEQ ID NOs: 87-94; and a CDRH3 comprising a sequence selected from SEQ ID NOs: 95-109.

[0101] In particular embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region comprising a CDRL1, a CDRL2, and a CDRL3, wherein: (a) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 5, 19, and 31, respectively; (b) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 6, 20, and 32, respectively; (c) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 6, 21, and 33, respectively; (d) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 6, 20, and 33, respectively; (e) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 7, 22, and 34, respectively; (f) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 8, 22, and 35, respectively; (g) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 9, 22, and 36, respectively; (h) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 10, 23, and 37, respectively; (i) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 11, 23, and 38, respectively; (j) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 12, 24, and 39, respectively; (k) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 13, 25, and 40, respectively; (l) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 14, 26, and 41, respectively; (m) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 15, 27, and 42, respectively; (n) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 28, and 43, respectively; (o) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 17, 29, and 44, respectively, or (p) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 18, 30, and 45, respectively.

[0102] In other particular embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a heavy chain variable region comprising a CDRH1, a CDRH2, and a CDRH3, wherein: (a) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 77, 87, and 95, respectively; (b) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 78, 88, and 96, respectively; (c) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 78, 88, and 97, respectively; (d) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 78, 89, and 96, respectively; (e) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 77, 90, and 98, respectively; (f) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 79, 90, and 99, respectively; (g) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 80, 91, and 100, respectively; (h) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 81, 91, and 101, respectively; (i) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 82, 92, and 102, respectively; (j) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 81, 91, and 103, respectively; (k) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 81, 91, and 104, respectively; (l) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 83, 93, and 105, respectively; (m) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 84, 91, and 106, respectively; (n) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 91, and 107, respectively; (o) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 86, 94, and 108, respectively; or (p) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 91, and 109, respectively.

[0103] In certain embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region comprising a CDRL1, a CDRL2, and a CDRL3 and a heavy chain variable region comprising a CDRH1, a CDRH2, and a CDRH3, wherein:

(a) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 5, 19, and 31, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 77, 87, and 95, respectively;

(b) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 6, 20, and 32, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 78, 88, and 96, respectively;

(c) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 6, 21, and 33, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 78, 88, and 97, respectively;

(d) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 6, 20, and 33, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 78, 88, and 97, respectively;

(e) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 6, 20, and 33, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 78, 89, and 96, respectively;

(f) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 7, 22, and 34, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 77, 87, and 95, respectively;

(g) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 8, 22, and 35, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 77, 90, and 98, respectively;

(h) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 9, 22, and 36, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 79, 90, and 99, respectively;

(i) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 10, 23, and 37, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 80, 91, and 100, respectively;

(j) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 10, 23, and 37, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 81, 91, and 101, respectively;

(k) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 11, 23, and 38, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 82, 92, and 102, respectively;

(l) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 12, 24, and 39, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 81, 91, and 103, respectively;

(m) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 13, 25, and 40, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 81, 91, and 104, respectively;

(n) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 14, 26, and 41, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 83, 93, and 105, respectively;

(o) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 15, 27, and 42, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 84, 91, and 106, respectively;

(p) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 28, and 43, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 91, and 107, respectively;

(q) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 17, 29, and 44, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 86, 94, and 108, respectively; or

(r) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 18, 30, and 45, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 91, and 109, respectively.

[0104] In one embodiment, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising a CDRL1, a CDRL2, and a CDRL3 and a heavy chain variable region comprising a CDRH1, a CDRH2, and a CDRH3, wherein CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 10, 23, and 37, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 80, 91, and 100, respectively. In another embodiment, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising a CDRL1, a CDRL2, and a CDRL3 and a heavy chain variable region comprising a CDRH1, a CDRH2, and a CDRH3, wherein CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 10, 23, and 37, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 81, 91, and 101, respectively. In yet another embodiment, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising a CDRL1, a CDRL2, and a CDRL3 and a heavy chain variable region comprising a CDRH1, a CDRH2, and a CDRH3, wherein CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 15, 27, and 42, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 84, 91, and 106, respectively. In still another embodiment, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising a CDRL1, a CDRL2, and a CDRL3 and a heavy chain variable region comprising a CDRH1, a CDRH2, and a CDRH3, wherein CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 28, and 43, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 91, and 107, respectively. In one particular embodiment, the TREM2 agonist antigen binding protein comprises a light

chain variable region comprising a CDRL1, a CDRL2, and a CDRL3 and a heavy chain variable region comprising a CDRH1, a CDRH2, and a CDRH3, wherein CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 17, 29, and 44, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 86, 94, and 108, respectively. In another particular embodiment, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising a CDRL1, a CDRL2, and a CDRL3 and a heavy chain variable region comprising a CDRH1, a CDRH2, and a CDRH3, wherein CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 8, 22, and 35, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 77, 90, and 98, respectively.

[0105] In certain embodiments, the TREM2 agonist antigen binding proteins of the invention comprise an immunoglobulin heavy chain variable region (VH) and an immunoglobulin light chain variable region (VL) from an antibody that specifically binds to human TREM2, such as the antibodies described herein. The “variable region,” used interchangeably herein with “variable domain” (variable region of a light chain (VL), variable region of a heavy chain (VH)), refers to the region in each of the light and heavy immunoglobulin chains which is involved directly in binding the antibody to the antigen. As discussed above, the regions of variable light and heavy chains have the same general structure and each region comprises four framework (FR) regions, the sequences of which are widely conserved, connected by three CDRs. The framework regions adopt a beta-sheet conformation and the CDRs may form loops connecting the beta-sheet structure. The CDRs in each chain are held in their three-dimensional structure by the framework regions and form, together with the CDRs from the other chain, the antigen binding site.

[0106] In some embodiments, the TREM2 agonist antigen binding proteins of the invention may comprise a light chain variable region selected from LV-01, LV-02, LV-03, LV-04, LV-05, LV-06, LV-07, LV-08, LV-09, LV-10, LV-11, LV-12, LV-13, LV-14, LV-15, LV-16, LV-17, and LV-18, as shown in Table 1A, and/or a heavy chain variable region selected from HV-01, HV-02, HV-03, HV-04, HV-05, HV-06, HV-07, HV-08, HV-09, HV-10, HV-11, HV-12, HV-13, HV-14, HV-15, HV-16, and HV-17, as shown in Table 1B, and functional fragments, derivatives, muteins and variants of these light chain and heavy chain variable regions.

[0107] Each of the light chain variable regions listed in Table 1A may be combined with any of the heavy chain variable regions listed in Table 1B to form an anti-TREM2 binding domain of the antigen binding proteins of the invention. Examples of such combinations

include, but are not limited to: LV-01 (SEQ ID NO: 46) and HV-01 (SEQ ID NO: 110); LV-02 (SEQ ID NO: 47) and HV-02 (SEQ ID NO: 111); LV-03 (SEQ ID NO: 48) and HV-03 (SEQ ID NO: 112); LV-04 (SEQ ID NO: 49) and HV-04 (SEQ ID NO: 113); LV-05 (SEQ ID NO: 50) and HV-05 (SEQ ID NO: 114); LV-06 (SEQ ID NO: 51) and HV-01 (SEQ ID NO: 110); LV-07 (SEQ ID NO: 52) and HV-06 (SEQ ID NO: 115); LV-08 (SEQ ID NO: 53) and HV-07 (SEQ ID NO: 116); LV-09 (SEQ ID NO: 54) and HV-08 (SEQ ID NO: 117); LV-10 (SEQ ID NO: 55) and HV-09 (SEQ ID NO: 118); LV-11 (SEQ ID NO: 56) and HV-10 (SEQ ID NO: 119); LV-12 (SEQ ID NO: 57) and HV-11 (SEQ ID NO: 120); LV-13 (SEQ ID NO: 58) and HV-12 (SEQ ID NO: 121); LV-14 (SEQ ID NO: 59) and HV-13 (SEQ ID NO: 122); LV-15 (SEQ ID NO: 60) and HV-14 (SEQ ID NO: 123); LV-16 (SEQ ID NO: 61) and HV-15 (SEQ ID NO: 124); LV-17 (SEQ ID NO: 62) and HV-16 (SEQ ID NO: 125); and LV-18 (SEQ ID NO: 63) and HV-17 (SEQ ID NO: 126).

[0108] In certain embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region comprising the sequence of LV-09 (SEQ ID NO: 54) and a heavy chain variable region comprising the sequence of HV-08 (SEQ ID NO: 117). In some embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region comprising the sequence of LV-10 (SEQ ID NO: 55) and a heavy chain variable region comprising the sequence of HV-09 (SEQ ID NO: 118). In other embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region comprising the sequence of LV-15 (SEQ ID NO: 60) and a heavy chain variable region comprising the sequence of HV-14 (SEQ ID NO: 123). In still other embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region comprising the sequence of LV-16 (SEQ ID NO: 61) and a heavy chain variable region comprising the sequence of HV-15 (SEQ ID NO: 124). In some embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region comprising the sequence of LV-17 (SEQ ID NO: 62) and a heavy chain variable region comprising the sequence of HV-16 (SEQ ID NO: 125). In certain embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region comprising the sequence of LV-07 (SEQ ID NO: 52) and a heavy chain variable region comprising the sequence of HV-06 (SEQ ID NO: 115).

[0109] In some embodiments, the TREM2 agonist antigen binding proteins comprise a light chain variable region comprising a sequence of contiguous amino acids that differs from the sequence of a light chain variable region in Table 1A, i.e. a VL selected from LV-01, LV-02,

LV-03, LV-04, LV-05, LV-06, LV-07, LV-08, LV-09, LV-10, LV-11, LV-12, LV-13, LV-14, LV-15, LV-16, LV-17, or LV-18, at only 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acid residues, wherein each such sequence difference is independently either a deletion, insertion or substitution of one amino acid, with the deletions, insertions and/or substitutions resulting in no more than 15 amino acid changes relative to the foregoing variable domain sequences. The light chain variable region in some TREM2 agonist antigen binding proteins comprises a sequence of amino acids that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97% or at least 99% sequence identity to the amino acid sequences of SEQ ID NOs: 46-63 (i.e. the light chain variable regions in Table 1A). In one embodiment, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising a sequence that is at least 90% identical to a sequence selected from SEQ ID NOs: 46-63. In another embodiment, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 46-63. In yet another embodiment, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising a sequence selected from SEQ ID NOs: 46-63. In some embodiments, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising a sequence of SEQ ID NO: 54. In other embodiments, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising a sequence of SEQ ID NO: 55. In yet other embodiments, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising a sequence of SEQ ID NO: 60. In still other embodiments, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising a sequence of SEQ ID NO: 61. In certain embodiments, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising a sequence of SEQ ID NO: 62. In other embodiments, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising a sequence of SEQ ID NO: 52.

[0110] In these and other embodiments, the TREM2 agonist antigen binding proteins comprise a heavy chain variable region comprising a sequence of contiguous amino acids that differs from the sequence of a heavy chain variable region in Table 1B, i.e., a VH selected from HV-01, HV-02, HV-03, HV-04, HV-05, HV-06, HV-07, HV-08, HV-09, HV-10, HV-11, HV-12, HV-13, HV-14, HV-15, HV-16, or HV-17, at only 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acid residues, wherein each such sequence difference is independently either a deletion, insertion or substitution of one amino acid, with the deletions, insertions

and/or substitutions resulting in no more than 15 amino acid changes relative to the foregoing variable domain sequences. The heavy chain variable region in some TREM2 agonist antigen binding proteins comprises a sequence of amino acids that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97% or at least 99% sequence identity to the amino acid sequences of SEQ ID NOs: 110-126 (i.e. the heavy chain variable regions in Table 1B). In one embodiment, the TREM2 agonist antigen binding protein comprises a heavy chain variable region comprising a sequence that is at least 90% identical to a sequence selected from SEQ ID NOs: 110-126. In another embodiment, the TREM2 agonist antigen binding protein comprises a heavy chain variable region comprising a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 110-126. In yet another embodiment, the TREM2 agonist antigen binding protein comprises a heavy chain variable region comprising a sequence selected from SEQ ID NOs: 110-126. In some embodiments, the TREM2 agonist antigen binding protein comprises a heavy chain variable region comprising a sequence of SEQ ID NO: 117. In other embodiments, the TREM2 agonist antigen binding protein comprises a heavy chain variable region comprising a sequence of SEQ ID NO: 118. In yet other embodiments, the TREM2 agonist antigen binding protein comprises a heavy chain variable region comprising a sequence of SEQ ID NO: 123. In still other embodiments, the TREM2 agonist antigen binding protein comprises a heavy chain variable region comprising a sequence of SEQ ID NO: 124. In certain embodiments, the TREM2 agonist antigen binding protein comprises a heavy chain variable region comprising a sequence of SEQ ID NO: 125. In other embodiments, the TREM2 agonist antigen binding protein comprises a heavy chain variable region comprising a sequence of SEQ ID NO: 115.

[0111] The term “identity,” as used herein, refers to a relationship between the sequences of two or more polypeptide molecules or two or more nucleic acid molecules, as determined by aligning and comparing the sequences. “Percent identity,” as used herein, means the percent of identical residues between the amino acids or nucleotides in the compared molecules and is calculated based on the size of the smallest of the molecules being compared. For these calculations, gaps in alignments (if any) must be addressed by a particular mathematical model or computer program (i.e., an “algorithm”). Methods that can be used to calculate the identity of the aligned nucleic acids or polypeptides include those described in *Computational Molecular Biology*, (Lesk, A. M., ed.), 1988, New York: Oxford University Press; *Biocomputing Informatics and Genome Projects*, (Smith, D. W., ed.), 1993, New York:

Academic Press; Computer Analysis of Sequence Data, Part I, (Griffin, A. M., and Griffin, H. G., eds.), 1994, New Jersey: Humana Press; von Heinje, G., 1987, Sequence Analysis in Molecular Biology, New York: Academic Press; Sequence Analysis Primer, (Gribskov, M. and Devereux, J., eds.), 1991, New York: M. Stockton Press; and Carillo et al., 1988, SIAM J. Applied Math. 48:1073. For example, sequence identity can be determined by standard methods that are commonly used to compare the similarity in position of the amino acids of two polypeptides. Using a computer program such as BLAST or FASTA, two polypeptide or two polynucleotide sequences are aligned for optimal matching of their respective residues (either along the full length of one or both sequences, or along a pre-determined portion of one or both sequences). The programs provide a default opening penalty and a default gap penalty, and a scoring matrix such as PAM 250 (Dayhoff et al., in Atlas of Protein Sequence and Structure, vol. 5, supp. 3, 1978) or BLOSUM62 (Henikoff et al., 1992, Proc. Natl. Acad. Sci. U.S.A. 89:10915-10919) can be used in conjunction with the computer program. For example, the percent identity can then be calculated as: the total number of identical matches multiplied by 100 and then divided by the sum of the length of the longer sequence within the matched span and the number of gaps introduced into the longer sequences in order to align the two sequences. In calculating percent identity, the sequences being compared are aligned in a way that gives the largest match between the sequences.

[0112] The GCG program package is a computer program that can be used to determine percent identity, which package includes GAP (Devereux et al., 1984, Nucl. Acid Res. 12:387; Genetics Computer Group, University of Wisconsin, Madison, WI). The computer algorithm GAP is used to align the two polypeptides or two polynucleotides for which the percent sequence identity is to be determined. The sequences are aligned for optimal matching of their respective amino acid or nucleotide (the “matched span”, as determined by the algorithm). A gap opening penalty (which is calculated as 3x the average diagonal, wherein the “average diagonal” is the average of the diagonal of the comparison matrix being used; the “diagonal” is the score or number assigned to each perfect amino acid match by the particular comparison matrix) and a gap extension penalty (which is usually 1/10 times the gap opening penalty), as well as a comparison matrix such as PAM 250 or BLOSUM 62 are used in conjunction with the algorithm. In certain embodiments, a standard comparison matrix (see, Dayhoff et al., 1978, Atlas of Protein Sequence and Structure 5:345-352 for the PAM 250 comparison matrix; Henikoff et al., 1992, Proc. Natl. Acad. Sci. U.S.A. 89:10915-10919 for the BLOSUM 62 comparison matrix) is also used by the algorithm.

[0113] Recommended parameters for determining percent identity for polypeptides or nucleotide sequences using the GAP program include the following:

Algorithm: Needleman et al., 1970, J. Mol. Biol. 48:443-453;

Comparison matrix: BLOSUM 62 from Henikoff et al., 1992, *supra*;

Gap Penalty: 12 (but with no penalty for end gaps)

Gap Length Penalty: 4

Threshold of Similarity: 0

[0114] Certain alignment schemes for aligning two amino acid sequences may result in matching of only a short region of the two sequences, and this small aligned region may have very high sequence identity even though there is no significant relationship between the two full-length sequences. Accordingly, the selected alignment method (GAP program) can be adjusted if so desired to result in an alignment that spans at least 50 contiguous amino acids of the target polypeptide.

[0115] Variants of the anti-TREM2 antibodies described herein can be generated by substituting one or more amino acids in the light chain or heavy chain variable regions to address chemical liabilities (e.g. aspartate isomerization, asparagine deamidation, tryptophan and methionine oxidation) or correct covariance violations (see WO 2012/125495, which is hereby incorporated by reference in its entirety) as described in Example 7. Such variants can have improved biophysical, expression, and/or stability properties as compared with the parental antibody. Thus, in some embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region and/or heavy chain variable region having one or more of the amino acid substitutions set forth in any of Tables 13-18.

[0116] Unless indicated otherwise by reference to a specific sequence, throughout the present specification and claims, the numbering of the amino acid residues in an immunoglobulin heavy chain or light chain is according to Kabat-EU numbering as described in Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed., US Department of Health and Human Services, NIH publication No. 91-3242, pp 662,680,689 (1991) and Edelman *et al.*, Proc. Natl. Acad. USA, Vol. 63: 78-85 (1969). The Kabat numbering scheme is typically used when referring to the position of an amino acid within the variable regions, whereas the EU numbering scheme is generally used when referring to the position of an amino acid with an immunoglobulin constant region. A chart summarizing correspondence between Kabat and EU numbering schemes with other numbering schemes is available on the IMGT® website (the international ImMunoGeneTics information system).

[0117] An amino acid substitution in an amino acid sequence is typically designated herein with a one-letter abbreviation for the amino acid residue in a particular position, followed by the numerical amino acid position relative to an original sequence of interest, which is then followed by the one-letter abbreviation for the amino acid residue substituted in. For example, “T30D” symbolizes a substitution of a threonine residue by an aspartate residue at amino acid position 30, relative to the original sequence of interest. Another example, “S218G” symbolizes a substitution of a serine residue by a glycine residue at amino acid position 218, relative to the original amino acid sequence of interest.

[0118] In some embodiments, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising the sequence of SEQ ID NO: 54 with a mutation at one or more amino acid positions 64, 79, 80, 85, 94, and/or 100. Such mutations can include V64G, V64A, Q79E, Q79D, S80P, S80A, F85V, F85L, F85A, F85D, F85I, F85L, F85M, F85T, W94F, W94Y, W94S, W94T, W94A, W94H, W94I, W94Q, P100R, P100Q, P100G, or combinations thereof. In these and other embodiments, the TREM2 agonist antigen binding protein comprises a heavy chain variable region comprising the sequence of SEQ ID NO: 117 with a mutation at one or more amino acid positions 19, 55, 56, 57, 58, and/or 104. In certain embodiments, the mutation is selected from M19K, M19R, M19T, M19E, M19N, M19Q, D55E, D55Q, D55N, D55T, S56A, S56Q, S56V, D57S, D57E, D57Q, T58A, T58V, W104F, W104Y, W104T, W104S, W104A, W104H, W104I, W104Q, or combinations thereof.

[0119] In other embodiments, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising the sequence of SEQ ID NO: 55 with a mutation at one or more amino acid positions 64, 79, 80, 94, and/or 100. In some embodiments, the mutation is selected from V64G, V64A, Q79E, Q79D, S80P, S80A, W94F, W94Y, W94S, W94T, W94A, W94H, W94I, W94Q, P100R, P100Q, P100G, or combinations thereof. In certain embodiments, the mutation is selected from V64G, V64A, Q79E, S80P, S80A, W94Y, W94S, P100R, P100Q, or combinations thereof. For instance, in some embodiments, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising the sequence of SEQ ID NO: 55 with one or more mutations selected from V64G, Q79E, S80P, W94Y, and P100Q. In these and other embodiments, the TREM2 agonist antigen binding protein comprises a heavy chain variable region comprising the sequence of SEQ ID NO: 118 with a mutation at one or more amino acid positions 19, 55, 56, 57, 58, and/or 104. Such mutations can include M19K, M19R, M19T, M19E, M19N, M19Q, D55E, D55Q, D55N, D55T, S56A, S56Q, S56V, D57S, D57E, D57Q, T58A, T58V, W104F, W104Y,

W104T, W104S, W104A, W104H, W104I, W104Q, or combinations thereof. In certain embodiments, the mutation is selected from M19K, D55E, S56A, D57E, T58A, W104Y, W104T, or combinations thereof.

[0120] In certain other embodiments, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising the sequence of SEQ ID NO: 60 with a mutation at one or more amino acid positions 60, 92, and/or 93. The mutation can be selected from L60S, L60P, L60D, L60A, D92E, D92Q, D92T, D92N, S93A, S93N, S93Q, S93V, or combinations thereof. In these and other embodiments, the TREM2 agonist antigen binding protein comprises a heavy chain variable region comprising the sequence of SEQ ID NO: 123 with a mutation at one or more amino acid positions 27, 55, 56, 57, 58, 105, and/or 106. In some embodiments, the mutation is selected from H27Y, H27D, H27F, H27N, D55E, D55Q, D55N, D55T, S56A, S56Q, S56V, D57S, D57E, D57Q, T58A, T58V, D105E, D105Q, D105T, D105N, D105G, S106A, S106Q, S106V, S106T, or combinations thereof.

[0121] In some embodiments, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising the sequence of SEQ ID NO: 61 with a mutation at one or more amino acid positions 56, 57, 92, and/or 93. In certain embodiments, the mutation is selected from N56S, N56T, N56Q, N56E, G57A, G57V, D92E, D92Q, D92T, D92N, S93A, S93N, S93Q, S93V, or combinations thereof. In some embodiments, the mutation is selected from N56S, N56Q, G57A, D92E, D92Q, S93A, or combinations thereof. In particular embodiments, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising the sequence of SEQ ID NO: 61 with one or more mutations selected from N56S, D92E, and S93A. In these and other embodiments, the TREM2 agonist antigen binding protein comprises a heavy chain variable region comprising the sequence of SEQ ID NO: 124 with a mutation at one or more amino acid positions 55, 56, 57, 58, 105, and/or 106. The mutation can be selected from D55E, D55Q, D55N, D55T, S56A, S56Q, S56V, D57S, D57E, D57Q, T58A, T58V, D105E, D105Q, D105T, D105N, D105G, S106A, S106Q, S106V, S106T, or combinations thereof. In certain embodiments, the mutation is D55E, D55Q, S56A, D57E, T58A, D105E, D105N, S106A, or combinations thereof. In some embodiments, the TREM2 agonist antigen binding protein comprises a heavy chain variable region comprising the sequence of SEQ ID NO: 124 with one or more mutations selected from D55E, S56A, D57E, D105E, and S106A.

[0122] In other embodiments, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising the sequence of SEQ ID NO: 62 with a mutation at amino

acid position 36, 46, 61 and/or 100. In particular embodiments, the mutation is selected from F36Y, S46L, S46R, S46V, S46F, K61R, P100Q, P100G, P100R or combinations thereof. In some embodiments, the mutation is F36Y, K61R, P100Q, or combinations thereof. In some embodiments, the mutation is S46L, P100Q, or combinations thereof. In these and other embodiments, the TREM2 agonist antigen binding protein comprises a heavy chain variable region comprising the sequence of SEQ ID NO: 125 with a mutation at one or more amino acid positions 43, 76, 85, 99, 100, and/or 116. The mutation can be selected from L43Q, L43K, L43H, I76T, R85S, R85G, R85N, R85D, D99E, D99Q, D99S, D99T, G100A, G100Y, G100V, T116L, T116M, T116P, T116R, or combinations thereof. In certain embodiments, the mutation is L43Q, I76T, R85S, D99E, G100A, G100Y, T116L, or combinations thereof.

[0123] In still other embodiments, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising the sequence of SEQ ID NO: 52 with a mutation at amino acid position 91. The mutation can be selected from F91V, F91I, F91T, F91L, or F91D. In one embodiment, the mutation is F91V. In these and other embodiments, the TREM2 agonist antigen binding protein comprises a heavy chain variable region comprising the sequence of SEQ ID NO: 115 with a mutation at amino acid position 62 and/or 63. In particular embodiments, the mutation is selected from D62E, D62Q, D62T, D62N, S63A, S63Q, S63V, or combinations thereof. In some embodiments, the mutation is selected from D62E, D62Q, S63A, or combinations thereof.

[0124] In certain embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region comprising the amino acid sequence of SEQ ID NO: 326 and a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 327. In certain embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region comprising the amino acid sequence of SEQ ID NO: 328 and a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 329. In certain embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region comprising the amino acid sequence of SEQ ID NO: 330 and a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 331. In certain embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region comprising the amino acid sequence of SEQ ID NO: 332 and a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 333.

[0125] In certain embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region consisting of or consisting essentially of the amino acid sequence of SEQ ID NO: 326, 328, 330 or 332. In certain embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a heavy chain variable region consisting of or consisting essentially of the amino acid sequence of SEQ ID NO: 327, 329, 331 or 333. In a specific embodiment, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region and a heavy chain variable region, wherein the light chain variable region consisting of or consisting essentially of the amino acid sequence of SEQ ID NO: 326 and the heavy chain variable region consisting of or consisting essentially of the amino acid sequence of SEQ ID NO: 327. In a specific embodiment, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region and a heavy chain variable region, wherein the light chain variable region consisting of or consisting essentially of the amino acid sequence of SEQ ID NO: 328 and the heavy chain variable region consisting of or consisting essentially of the amino acid sequence of SEQ ID NO: 329. In a specific embodiment, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region and a heavy chain variable region, wherein the light chain variable region consisting of or consisting essentially of the amino acid sequence of SEQ ID NO: 330 and the heavy chain variable region consisting of or consisting essentially of the amino acid sequence of SEQ ID NO: 331. In a specific embodiment, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region and a heavy chain variable region, wherein the light chain variable region consisting of or consisting essentially of the amino acid sequence of SEQ ID NO: 332 and the heavy chain variable region consisting of or consisting essentially of the amino acid sequence of SEQ ID NO: 333.

[0126] Additional variants of the anti-TREM2 antibodies described herein can be generated by affinity modulating any of the anti-TREM2 antibodies described herein. An “affinity-modulated antibody” is an antibody that comprises one or more amino acid substitutions in its light chain variable region sequence and/or heavy chain variable region sequence that increases or decreases the affinity of the antibody for the target antigen as compared to the parental antibody that does not contain the amino acid substitutions. Antibody affinity modulation methods are known to those of skill in the art and can include CDR walking mutagenesis (Yang et al., J. Mol. Biol., 254, 392-403, 1995), chain shuffling (Marks et al., Bio/Technology, 10, 779-783, 1992), use of mutation strains of *E. coli* (Low et al., J. Mol.

Biol., 250, 350-368, 1996), DNA shuffling (Patten et al., Curr. Opin. Biotechnol., 8, 724-733, 1997), phage display (Thompson et al., J. Mol. Biol., 256, 7-88, 1996), PCR techniques (Cramer, et al., Nature, 391, 288-291, 1998), and other mutagenesis strategies (Barbas et al. Proc Nat. Acad. Sci. USA 91:3809-3813, 1994; Schier et al. Gene 169:147-155, 1995; Yelton et al. J. Immunol. 155:1994-2004, 1995; Jackson et al., J. Immunol. 154(7):3310-9, 1995; and Hawkins et al, J. Mol. Biol. 226:889-896, 1992). Methods of affinity modulation are discussed in Hoogenboom, Trends in Biotechnology, Vol. 15: 62-70, 1995 and Vaughan *et al.*, Nature Biotechnology, 16: 535-539, 1998. One specific method for generating affinity-modulated variants of the anti-TREM2 antibodies described herein is the use of a yeast-display Fab mutagenesis library as described in Example 8.

[0127] In certain embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region and/or heavy chain variable region from an affinity-modulated variant of the 6E7 antibody (Example 8). For instance, in some embodiments, the TREM2 agonist antigen binding proteins comprise a light chain variable region and/or a heavy chain variable region having one or more of the amino acid substitutions set forth in Table 23. In one embodiment, the TREM2 agonist antigen binding protein comprises a light chain variable region comprising the sequence of SEQ ID NO: 61 with a mutation at one or more amino acid positions 24, 31, 50, 52, 54, 56, 89, 92, 93, 94 and/or 96. In certain embodiments, the mutation is selected from R24A, S31R, A50S, A50G, S52G, L54R, N56K, N56R, N56L, N56T, Q89G, D92V, S93R, F94Y, F94L, R96H, R96L, or combinations thereof. In these and other embodiments, the TREM2 agonist antigen binding protein comprises a heavy chain variable region comprising the sequence of SEQ ID NO: 124 with a mutation at one or more amino acid positions 27, 28, 30, 32, 50, 54, 58, 60, 61, 63, 66, 99, 101, 103, 104, and/or 110. In some embodiments, the mutation is selected from Y27S, S28G, S28H, T30N, T30G, T30E, T30A, Y32E, I50T, G54S, T58V, Y60L, S61A, S63G, S63E, G66D, Q99G, Q99S, Q99M, T101G, Y103R, Y104G, F110S, or combinations thereof. Amino acid sequences for light chain and heavy chain variable regions and associated CDRs of exemplary variants of the 6E7 antibody with improved affinity are set forth below in Tables 2A and 2B, respectively. Amino acid sequences for light chain and heavy chain variable regions and associated CDRs of exemplary variants of the 6E7 antibody with reduced affinity are set forth below in Tables 3A and 3B, respectively. The corresponding sequences for the 6E7 antibody are listed for comparison.

Table 2A. Light Chain Variable Region Amino Acid Sequences for Improved Affinity TREM2 Antibodies

Variant Ab ID.	VL Group	VL Amino Acid Sequence	CDRL1	CDRL2	CDRL3
6E7	LV-16	DIQMTQSPSSVSASVGDRVITIT CRASQGISSWLAWYQQKPGK APKLLIYAASSLQNGVPSRFSG SGSGTDFTLTISLQPEDFATYF CQQADSFPRTFGQGTKLEIK (SEQ ID NO: 61)	RASQGISSWLA (SEQ ID NO: 16)	AASSLQN (SEQ ID NO: 28)	QQADSFPRT (SEQ ID NO: 43)
V3	LV-101	DIQMTQSPSSVSASVGDRVITIT CRASQGISSWLAWYQQKPGK APKLLIYAASSRQNGVPSRFSG SGSGTDFTLTISLQPEDFATYF CQQADRFPRTFGQGTKLEIK (SEQ ID NO: 153)	RASQGISSWLA (SEQ ID NO: 16)	AASSRQN (SEQ ID NO: 143)	QQADRFPRT (SEQ ID NO: 148)
V24	LV-102	DIQMTQSPSSVSASVGDRVITIT CRASQGISSWLAWYQQKPGK APKLLIYAASSLQKGVPSRFSG SGSGTDFTLTISLQPEDFATYF CQQADSFPHTFGQGTKLEIK (SEQ ID NO: 154)	RASQGISSWLA (SEQ ID NO: 16)	AASSLQK (SEQ ID NO: 144)	QQADSFPHT (SEQ ID NO: 149)
V27	LV-103	DIQMTQSPSSVSASVGDRVITIT CRASQGISSWLAWYQQKPGK APKLLIYAASSLQKGVPSRFSG SGSGTDFTLTISLQPEDFATYF CQQADSFPRTFGQGTKLEIK (SEQ ID NO: 155)	RASQGISSWLA (SEQ ID NO: 16)	AASSLQR (SEQ ID NO: 145)	QQADSFPRT (SEQ ID NO: 43)
V40	LV-104	DIQMTQSPSSVSASVGDRVITIT CRASQGISSWLAWYQQKPGK APKLLIYAASSLQLGVPSRFSG SGSGTDFTLTISLQPEDFATYF CQQADRFPRTFGQGTKLEIK (SEQ ID NO: 156)	RASQGISSWLA (SEQ ID NO: 16)	AASSLQL (SEQ ID NO: 146)	QQADRFPRT (SEQ ID NO: 148)
V48	LV-105	DIQMTQSPSSVSASVGDRVITIT CRASQGISSWLAWYQQKPGK APKLLIYAASSLQTGVPSRFSG SGSGTDFTLTISLQPEDFATYF CQQADSLPRTFGQGTKLEIK (SEQ ID NO: 157)	RASQGISSWLA (SEQ ID NO: 16)	AASSLQT (SEQ ID NO: 26)	QQADSLPRT (SEQ ID NO: 150)
V49 V73	LV-106	DIQMTQSPSSVSASVGDRVITIT CRASQGISSWLAWYQQKPGK APKLLIYAASSRQNGVPSRFSG SGSGTDFTLTISLQPEDFATYF CQQADSYPRTFGQGTKLEIK (SEQ ID NO: 158)	RASQGISSWLA (SEQ ID NO: 16)	AASSRQN (SEQ ID NO: 143)	QQADSYPRT (SEQ ID NO: 151)
V52	LV-107	DIQMTQSPSSVSASVGDRVITIT CRASQGISSWLAWYQQKPGK APKLLIYAASSLQKGVPSRFSG SGSGTDFTLTISLQPEDFATYF CQQADRFPRTFGQGTKLEIK (SEQ ID NO: 159)	RASQGISSWLA (SEQ ID NO: 16)	AASSLQR (SEQ ID NO: 145)	QQADRFPRT (SEQ ID NO: 148)
V60	LV-108	DIQMTQSPSSVSASVGDRVITIT CRASQGISSWLAWYQQKPGK APKLLIYAASSLQKGVPSRFSG SGSGTDFTLTISLQPEDFATYF CGQADSFPRTFGQGTKLEIK (SEQ ID NO: 160)	RASQGISSWLA (SEQ ID NO: 16)	AASSLQR (SEQ ID NO: 145)	CGQADSFPRT (SEQ ID NO: 152)

Variant Ab ID.	VL Group	VL Amino Acid Sequence	CDRL1	CDRL2	CDRL3
V76	LV-109	DIQMTQSPSSVSASVGDRVTIT CRASQGISSWLAWYQQKPGK APKLLIYAASSLQKGVPSRFSG SGSGRDFTLTISSLQPEDFATYF CQQADSFPRTFGQGTKLEIK (SEQ ID NO: 161)	RASQGISSWLA (SEQ ID NO: 16)	AASSLQK (SEQ ID NO: 144)	QQADSFPRT (SEQ ID NO: 43)
V84	LV-110	DIQMTQSPSSVSASVGDRVTIT CRASQGISSWLAWYQQKPGK APKLLIYGASSLQNGVPSRFSG SGSGTDFTLTISSLQPEDFATYF CQQADSFPRTFGQGTKLEIK (SEQ ID NO: 162)	RASQGISSWLA (SEQ ID NO: 16)	GASSLQN (SEQ ID NO: 147)	QQADSFPRT (SEQ ID NO: 43)

Table 2B. Heavy Chain Variable Region Amino Acid Sequences for Improved Affinity TREM2 Antibodies

Variant Ab ID.	VH Group	VH Amino Acid Sequence	FR1/CDRH1 Border	CDRH1	CDRH2	CDRH3
6E7	HV-15	EVQLVQSGAEV KKPGESLKISCK GSGYSFTSYWIA WVRQMPGKGLE WMGHIYPGSDT RYSFSFQGGVTI SADKSISTAYLQ WSSLKASDTAM YFCARQRTFYY DSSDYFDYWGG GTLVTVSS (SEQ ID NO: 124)	YSFT (SEQ ID NO: 163)	SYWIA (SEQ ID NO: 85)	IIYPGDS DTRYSPSFQG (SEQ ID NO: 91)	QRTFYYDSSDYFDY (SEQ ID NO: 107)
V3	HV-101	EVQLVQSGAEV KKPGESLKISCK GSGYSFASYWIA WVRQMPGKGLE WMGHIYPGSDT RYSFSFQGGVTI SADKSISTAYLQ WSSLKASDTAM YFCARGRTFYY DSSDYFDYWGG GTLVTVSS (SEQ ID NO: 180)	YSFA (SEQ ID NO: 164)	SYWIA (SEQ ID NO: 85)	IIYPGDS DTRYSPSFQD (SEQ ID NO: 170)	GRTFYYDSSDYFDY (SEQ ID NO: 176)
V24	HV-102	EVQLVQSGAEV KKPGESLKISCK GSGYSFTSYWIA WVRQMPGKGLE WMGHIYPGSD VRYSFSFQGGVT ISADKSISTAYLQ WSSLKASDTAM YFCARSRTFYYD SSDYFDYWGG TLVTVSS (SEQ ID NO: 181)	YSFT (SEQ ID NO: 163)	SYWIA (SEQ ID NO: 85)	IIYPGDS DTRYSPSFQG (SEQ ID NO: 171)	SRTFYYDSSDYFDY (SEQ ID NO: 177)

Variant Ab ID.	VH Group	VH Amino Acid Sequence	FR1/ CDRH1 Border	CDRH1	CDRH2	CDRH3
V27	HV-103	EVQLVQSGAEV KKPGESLKISCK GSGYSFTSYWIA WVRQMPGKGLE WMGHYPGDSDT RYAPSFQGQVTI SADKSISTAYLQ WSSLKASDTAM YFCVRSRTFYFD SSDYFDYWGQG TLVTVSS (SEQ ID NO: 182)	YSFT (SEQ ID NO: 163)	SYWIA (SEQ ID NO: 85)	IIYPGDSDDRYAPSFQG (SEQ ID NO: 172)	SRTFYFDSSDYFDY (SEQ ID NO: 177)
V40	HV-104	EVQLVQSGAEV KKPGESLKISCK GSGYSFGSYWIA WVRQMPGKGLE WMGHYPGDS VRYSFSGQGQVT ISADKSISTAYLQ WSSLKASDTAM YFCARQRTFY DSSDYSDYWGQ GTLVTVSS (SEQ ID NO: 183)	YSFG (SEQ ID NO: 165)	SYWIA (SEQ ID NO: 85)	IIYPGDSDDRYSPSFQG (SEQ ID NO: 171)	QRTFYDSSDYSDY (SEQ ID NO: 178)
V48	HV-105	EVQLVQSGAEV KKPGESLKISCK GSGYSFGSYWIA WVRQMPGKGLE WMGHYPGDS VRYSFSGQGQVT ISADKSISTAYLQ WSSLKASDTAM YFCARMRTFY DSSDYFDYWGQ GTLVTVSS (SEQ ID NO: 184)	YSFG (SEQ ID NO: 165)	SYWIA (SEQ ID NO: 85)	IIYPGDSDDRYSPSFQG (SEQ ID NO: 171)	MRTFYDSSDYFDY (SEQ ID NO: 179)
V49	HV-106	EVQLVQSGAEV KKPGESLKISCK GSGYSFNSYWIA WVRQMPGKGLE WMGTIYPGDS TRLSPSFQGQVT ISADKSISTAYLQ WSSLKASDTAM YFCARSRTFYD SSDYFDYWGQG TLVTVSS (SEQ ID NO: 185)	YSFN (SEQ ID NO: 166)	SYWIA (SEQ ID NO: 85)	TIYPGDSDDRLSPSFQG (SEQ ID NO: 173)	SRTFYDSSDYFDY (SEQ ID NO: 177)
V52	HV-107	EVQLVQSGAEV KKPGESLKISCK GSGYSFESYWIA	YSFE (SEQ ID NO: 167)	SYWIA (SEQ ID NO: 85)	IIYPGDSDDRYSPSFQG (SEQ ID NO: 91)	GRTFYDSSDYFDY (SEQ ID NO: 176)

Variant Ab ID.	VH Group	VH Amino Acid Sequence	FR1/ CDRH1 Border	CDRH1	CDRH2	CDRH3
		WVRQMPGKGLE WMGHIYPGDSDT RYSFSFQGGVTI SADKSISTAYLQ WSSLKASDTAM YFCARGRTFY DSSDYFDYWGQ GTLVTVSS (SEQ ID NO: 186)				
V60	HV-108	EVQLVQSGAEV KKPGESLKISCK GSGYHFTSYWIA WVRQMPGKGLE WMGHIYPGDS VRYSFSFQGGVT ISADKSISTAYLQ WSSLKASDTAM YFCARQRTFY DSSDYSDYWGQ GTLVTVSS (SEQ ID NO: 187)	YHFT (SEQ ID NO: 168)	SYWIA (SEQ ID NO: 85)	IIYPGDS D V R Y S P S F Q G (SEQ ID NO: 171)	QRTFY Y D S S D Y S D Y (SEQ ID NO: 178)
V73	HV-109	EVQLVQSGAEV KKPGESLKISCK GSGYSFGSYWIA WVRQMPGKGLE WMGHIYPGDSDT RYSFGFQGGVTI SADKSISTAYLQ WSSLKASDTAM YFCARGRTFY DSSDYFDYWGQ GTLVTVSS (SEQ ID NO: 188)	YSFG (SEQ ID NO: 165)	SYWIA (SEQ ID NO: 85)	IIYPGDS D T R Y S P G F Q G (SEQ ID NO: 174)	GRTFY Y D S S D Y F D Y (SEQ ID NO: 176)
V76	HV-110	EVQLVQSGAEV KKPGESLKISCK GSGYSFGSYWIA WVRQMPGKGLE WMGHIYPGDSDT RYSPEFQGGVTI SADKSISTAYLQ WSSLKASDTAM YFCARQRTFY DSSDYSDYWGQ GTLVTVSS (SEQ ID NO: 189)	YSFG (SEQ ID NO: 165)	SYWIA (SEQ ID NO: 85)	IIYPGDS D T R Y S P E F Q G (SEQ ID NO: 175)	QRTFY Y D S S D Y S D Y (SEQ ID NO: 178)
V84	HV-111	EVQLVQSGAEV KKPGESLKISCK GSGYGFTSYWIA WVRQMPGKGLE WMGHIYPGDSDT RYSFSFQGGVTI SADKSISTAYLQ	YGFT (SEQ ID NO: 169)	SYWIA (SEQ ID NO: 85)	IIYPGDS D T R Y S P S F Q G (SEQ ID NO: 91)	QRTFY Y D S S D Y S D Y (SEQ ID NO: 178)

Variant Ab ID.	VH Group	VH Amino Acid Sequence	FR1/CDRH1 Border	CDRH1	CDRH2	CDRH3
		WSSLKASDTAM YFCARQRTFYY DSSDYSDYWGQ GTLVTVSS (SEQ ID NO: 190)				

[0128] The TREM2 agonist antigen binding proteins of the invention may comprise one or more of the CDRs from the improved affinity variants presented in Table 2A (light chain CDRs; i.e. CDRLs) and Table 2B (heavy chain CDRs, i.e. CDRHs). In some embodiments, the TREM2 agonist antigen binding proteins comprise a consensus CDR sequence derived from the improved affinity variants. For instance, in one embodiment, the TREM2 agonist antigen binding proteins comprise a CDRL2 consensus sequence of $X_1ASSX_2QX_3$ (SEQ ID NO: 139), where X_1 is A or G; X_2 is L or R; and X_3 is N, K, R, L, or T. In another embodiment, the TREM2 agonist antigen binding proteins comprise a CDRL3 consensus sequence of $X_1QADX_2X_3PX_4T$ (SEQ ID NO: 140), where X_1 is Q or G; X_2 is S or R; X_3 is F, L, or Y; and X_4 is R or H. In yet another embodiment, the TREM2 agonist antigen binding proteins comprise a CDRH2 consensus sequence of $X_1IYPGDSDX_2RX_3X_4PX_5FQX_6$ (SEQ ID NO: 141), where X_1 is I or T; X_2 is T or V; X_3 is Y or L; X_4 is S or A; X_5 is S, G, or E; and X_6 is G or D. In still another embodiment, the TREM2 agonist antigen binding proteins comprise a CDRH3 consensus sequence of $X_1RTFYDSSDYX_2DY$ (SEQ ID NO: 142), where X_1 is Q, G, S, or M; and X_2 is F or S. In certain embodiments, the TREM2 agonist antigen binding proteins comprise a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3, wherein CDRL1 comprises the sequence of SEQ ID NO: 16, CDRL2 comprises the consensus sequence of SEQ ID NO: 139, CDRL3 comprises the consensus sequence of SEQ ID NO: 140, CDRH1 comprises the sequence of SEQ ID NO: 85, CDRH2 comprises the consensus sequence of SEQ ID NO: 141, and CDRH3 comprises the consensus sequence of SEQ ID NO: 142.

[0129] In some embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a CDRL1 comprising the sequence of SEQ ID NO: 16; a CDRL2 comprising a sequence selected from SEQ ID NOs: 26 and 143-147; a CDRL3 comprising a sequence selected from SEQ ID NOs: 43 and 148-152; a CDRH1 comprising the sequence of SEQ ID

NO: 85; a CDRH2 comprising a sequence selected from SEQ ID NOs: 91 and 170-175; and a CDRH3 comprising a sequence selected from SEQ ID NOs: 176-179.

[0130] In particular embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region comprising a CDRL1, a CDRL2, and a CDRL3, wherein: (a) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 143, and 148, respectively; (b) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 144, and 149, respectively; (c) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 145, and 43, respectively; (d) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 146, and 148, respectively; (e) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 26, and 150, respectively; (f) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 143, and 151, respectively; (g) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 145, and 148, respectively; (h) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 145, and 152, respectively; (i) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 144, and 43, respectively; or (j) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 147, and 43, respectively.

[0131] In related embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a heavy chain variable region comprising a CDRH1, a CDRH2, and a CDRH3, wherein: (a) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 170, and 176, respectively; (b) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 171, and 177, respectively; (c) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 172, and 177, respectively; (d) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 171, and 178, respectively; (e) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 171, and 179, respectively; (f) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 173, and 177, respectively; (g) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 91, and 176, respectively; (h) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 174, and 176, respectively; (i) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 175, and 178, respectively; or (j) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 91, and 178, respectively.

[0132] In certain embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region comprising a CDRL1, a CDRL2, and a CDRL3 and a heavy chain variable region comprising a CDRH1, a CDRH2, and a CDRH3, wherein:

(a) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 143, and 148, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 170, and 176, respectively;

(b) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 144, and 149, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 171, and 177, respectively;

(c) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 145, and 43, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 172, and 177, respectively;

(d) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 146, and 148, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 171, and 178, respectively;

(e) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 26, and 150, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 171, and 179, respectively;

(f) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 143, and 151, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 173, and 177, respectively;

(g) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 145, and 148, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 91, and 176, respectively;

(h) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 145, and 152, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 171, and 178, respectively;

(i) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 143, and 151, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 174, and 176, respectively;

(j) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 144, and 43, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 175, and 178, respectively; or

(k) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 147, and 43, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 91, and 178, respectively.

[0133] In some embodiments, the TREM2 agonist antigen binding proteins of the invention may comprise a light chain variable region selected from LV-101, LV-102, LV-103, LV-104, LV-105, LV-106, LV-107, LV-108, LV-109, and LV-110, as shown in Table 2A, and/or a heavy chain variable region selected from HV-101, HV-102, HV-103, HV-104, HV-105, HV-106, HV-107, HV-108, HV-109, HV-110, and HV-111, as shown in Table 2B, or sequences that are at least 80% identical, at least 85% identical, at least 90% identical, or at least 95% identical to any of the sequences in Tables 2A and 2B. For instance, in certain embodiments, the TREM2 agonist antigen binding proteins comprise a light chain variable region comprising (i) a sequence that is at least 90% identical to a sequence selected from SEQ ID NOs: 153-162, (ii) a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 153-162, or (iii) a sequence selected from SEQ ID NOs: 153-162. In related embodiments, the TREM2 agonist antigen binding proteins comprise a heavy chain variable region comprising (i) a sequence that is at least 90% identical to a sequence selected from SEQ ID NOs: 180-190, (ii) a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 180-190, or (iii) a sequence selected from SEQ ID NOs: 180-190.

[0134] Each of the light chain variable regions listed in Table 2A may be combined with any of the heavy chain variable regions listed in Table 2B to form an anti-TREM2 binding domain of the antigen binding proteins of the invention. Examples of such combinations include, but are not limited to: LV-101 (SEQ ID NO: 153) and HV-101 (SEQ ID NO: 180); LV-102 (SEQ ID NO: 154) and HV-102 (SEQ ID NO: 181); LV-103 (SEQ ID NO: 155) and HV-103 (SEQ ID NO: 182); LV-104 (SEQ ID NO: 156) and HV-104 (SEQ ID NO: 183); LV-105 (SEQ ID NO: 157) and HV-105 (SEQ ID NO: 184); LV-106 (SEQ ID NO: 158) and HV-106 (SEQ ID NO: 185); LV-107 (SEQ ID NO: 159) and HV-107 (SEQ ID NO: 186); LV-108 (SEQ ID NO: 160) and HV-108 (SEQ ID NO: 187); LV-106 (SEQ ID NO: 158) and HV-109 (SEQ ID NO: 188); LV-109 (SEQ ID NO: 161) and HV-110 (SEQ ID NO: 189); and LV-110 (SEQ ID NO: 162) and HV-111 (SEQ ID NO: 190).

Table 3A. Light Chain Variable Region Amino Acid Sequences for Reduced Affinity TREM2 Antibodies

Variant Ab ID.	VL Group	VL Amino Acid Sequence	CDRL1	CDRL2	CDRL3
6E7	LV-16	DIQMTQSPSSVSASVGDRV ITCRASQGISSWLAWYQQK PKAPKLLIYAASSLQNGVPS RFGSGSGTDFLTISLQPE	RASQGISSWLA (SEQ ID NO: 16)	AASSLQN (SEQ ID NO: 28)	QQADSFPR (SEQ ID NO: 43)

Variant Ab ID.	VL Group	VL Amino Acid Sequence	CDRL1	CDRL2	CDRL3
		DFATYFCQQADSFPRTFGQG TKLEIK (SEQ ID NO: 61)			
V9 V30 V33 V44 V68	LV-16	DIQMTQSPSSVSASVGDRVT ITCRASQGISSWLAWYQQKP GKAPKLLIYAASSLQNGVPS RFSGSGSGTDFTLTISSLQPE DFATYFCQQADSFPRTFGQG TKLEIK (SEQ ID NO: 61)	RASQGISSWLA (SEQ ID NO: 16)	AASSLQN (SEQ ID NO: 28)	QQADSFPRT (SEQ ID NO: 43)
V10	LV-201	DIQMTQSPSSVSASVGDRVT ITCRASQGISSWLAWYQQKP GKAPKLLIYSASSLQNGVPS RFSGSGSGTDFTLTISSLQPE DFATYFCQQADSFPRTFGQG TKLEIK (SEQ ID NO: 295)	RASQGISSWLA (SEQ ID NO: 16)	SASSLQN (SEQ ID NO: 292)	QQADSFPRT (SEQ ID NO: 43)
V23	LV-202	DIQMTQSPSSVSASVGDRVT ITCRASQGISSWLAWYQQKP GKAPKLLIYAASSLQNGVPS RFSGSGSGTDFTLTISSLQPE DFATYFCQQADSFPLTFGQG TKLEIK (SEQ ID NO: 296)	RASQGISSWLA (SEQ ID NO: 16)	AASSLQN (SEQ ID NO: 28)	QQADSFPLT (SEQ ID NO: 294)
V57	LV-203	DIQMTQSPSSVSASVGDRVT ITCAASQGISSWLAWYQQKP GKAPKLLIYAASSLQNGVPS RFSGSGSGTDFTLTISSLQPE DFATYFCQQADSFPRTFGQG TKLEIK (SEQ ID NO: 297)	AASQGISSWLA (SEQ ID NO: 290)	AASSLQN (SEQ ID NO: 28)	QQADSFPRT (SEQ ID NO: 43)
V70	LV-204	DIQMTQSPSSVSASVGDRVT ITCRASQGISSWLAWYQQKP GKAPKLLIYAAGSLQNGVPS RFSGSGSGTDFTLTISSLQPE DFATYFCQQADSFPRTFGQG TKLEIK (SEQ ID NO: 298)	RASQGISSWLA (SEQ ID NO: 16)	AAGSLQN (SEQ ID NO: 293)	QQADSFPRT (SEQ ID NO: 43)
V83	LV-205	DIQMTQSPSSVSASVGDRVT ITCRASQGISSWLAWYQQKP GKAPKLLIYAASSLQNGVPS RFSGSGSGTDFTLTISSLQPE DFATYFCQQAVSFPRTFGQG TKLEIK (SEQ ID NO: 299)	RASQGISSWLA (SEQ ID NO: 16)	AASSLQN (SEQ ID NO: 28)	QQAVSFPRT (SEQ ID NO: 271)
V90	LV-206	DIQMTQSPSSVSASVGDRVT ITCRASQGISRWLAWYQQK PGKAPKLLIYAASSLQNGVP SRFSGSGSGTDFTLTISSLQP EDFATYFCQQADSFPRTFGQ GTKLEIK (SEQ ID NO: 300)	RASQGISRWLA (SEQ ID NO: 291)	AASSLQN (SEQ ID NO: 28)	QQADSFPRT (SEQ ID NO: 43)

Table 3B. Heavy Chain Variable Region Amino Acid Sequences for Reduced Affinity TREM2 Antibodies

Variant Ab ID.	VH Group	VH Amino Acid Sequence	FR1/CDRH1 border	CDRH1	CDRH2	CDRH3
6E7	HV-15	EVQLVQSGAEV KKGESLKISCK GSGYSFTSYWIA WVRQMPGKGLE WMGIYPGSDT	YSFT (SEQ ID NO: 163)	SYWIA (SEQ ID NO: 85)	IYPGDS DTRYSPSFQG (SEQ ID NO: 91)	QRTFYDSSDYFDY (SEQ ID NO: 107)

Variant Ab ID.	VH Group	VH Amino Acid Sequence	FR1/CDRH1 border	CDRH1	CDRH2	CDRH3
		RYSPSFQGGQVTI SADKSISTAYLQ WSSLKASDTAM YFCARQRTFYY DSSDYFDYWGQ GTLVTVSS (SEQ ID NO: 124)				
V9	HV-201	EVQLVQSGAEV KKPGESLKISCK GSGYSFTSYWIA WVRQMPGKGLE WMGHIYPGDSDT RYSPSFQGGQVTI SADKSISTAYLQ WSSLKASDTAM YFCARQRTFYY DSSDYFDYWGQ GTLVTVSS (SEQ ID NO: 307)	YSFT (SEQ ID NO: 163)	SYWIA (SEQ ID NO: 85)	IIYPGDS DTRYSPSFQG (SEQ ID NO: 91)	QRGFYYDSSDYFDY (SEQ ID NO: 304)
V10 V23 V57 V70 V83	HV-15	EVQLVQSGAEV KKPGESLKISCK GSGYSFTSYWIA WVRQMPGKGLE WMGHIYPGDSDT RYSPSFQGGQVTI SADKSISTAYLQ WSSLKASDTAM YFCARQRTFYY DSSDYFDYWGQ GTLVTVSS (SEQ ID NO: 124)	YSFT (SEQ ID NO: 163)	SYWIA (SEQ ID NO: 85)	IIYPGDS DTRYSPSFQG (SEQ ID NO: 91)	QRTFYYDSSDYFDY (SEQ ID NO: 107)
V30	HV-202	EVQLVQSGAEV KKPGESLKISCK GSGSFTSYWIA WVRQMPGKGLE WMGHIYPGDSDT RYSPSFQGGQVTI SADKSISTAYLQ WSSLKASDTAM YFCARQRTFYY DSSDYFDYWGQ GTLVTVSS (SEQ ID NO: 308)	SSFT (SEQ ID NO: 301)	SYWIA (SEQ ID NO: 85)	IIYPGDS DTRYSPSFQG (SEQ ID NO: 91)	QRTFYYDSSDYFDY (SEQ ID NO: 107)
V33	HV-203	EVQLVQSGAEV KKPGESLKISCK GSGYSFTSYWIA WVRQMPGKGLE WMGHIYPGDSDT RYSPSFQGGQVTI SADKSISTAYLQ WSSLKASDTAM YFCARQRTFYG DSSDYFDYWGQ GTLVTVSS (SEQ ID NO: 309)	YSFT (SEQ ID NO: 163)	SYWIA (SEQ ID NO: 85)	IIYPGDS DTRYSPSFQG (SEQ ID NO: 91)	QRTFYGDSSDYFDY (SEQ ID NO: 305)

Variant Ab ID.	VH Group	VH Amino Acid Sequence	FR1/CDRH1 border	CDRH1	CDRH2	CDRH3
V44	HV-204	EVQLVQSGAEV KKPGESLKISCK GSGYSFTSYWIA WVRQMPGKGLE WMGHIYPGSDST RYSPSFQGGQVTI SADKSISTAYLQ WSSLKASDTAM YFCARQRTFYY DSSDYFDYWGQ GTLVTVSS (SEQ ID NO: 310)	YSFT (SEQ ID NO: 163)	SYWIA (SEQ ID NO: 85)	IIYPSDSDTRYSPSFQG (SEQ ID NO: 303)	QRTFYYDSSDYFDY (SEQ ID NO: 107)
V68	HV-205	EVQLVQSGAEV KKPGESLKISCK GSGYSFTSYWIA WVRQMPGKGLE WMGHIYPGSDST RYSPSFQGGQVTI SADKSISTAYLQ WSSLKASDTAM YFCARQRTFRY DSSDYFDYWGQ GTLVTVSS (SEQ ID NO: 311)	YSFT (SEQ ID NO: 163)	SYWIA (SEQ ID NO: 85)	IIYPGDS DTRYSPSFQG (SEQ ID NO: 91)	QRTFRYDSSDYFDY (SEQ ID NO: 306)
V90	HV-206	EVQLVQSGAEV KKPGESLKISCK GSGYSFTSEWIA WVRQMPGKGLE WMGHIYPGSDST RYSPSFQGGQVTI SADKSISTAYLQ WSSLKASDTAM YFCARQRTFYY DSSDYFDYWGQ GTLVTVSS (SEQ ID NO: 312)	YSFT (SEQ ID NO: 163)	SEWIA (SEQ ID NO: 302)	IIYPGDS DTRYSPSFQG (SEQ ID NO: 91)	QRTFYYDSSDYFDY (SEQ ID NO: 107)

[0135] The TREM2 agonist antigen binding proteins of the invention may comprise one or more of the CDRs from the reduced affinity variants presented in Table 3A (light chain CDRs; i.e. CDRLs) and Table 3B (heavy chain CDRs, i.e. CDRHs). In some embodiments, the TREM2 agonist antigen binding proteins comprise a consensus CDR sequence derived from the reduced affinity variants. For instance, in one embodiment, the TREM2 agonist antigen binding proteins comprise a CDRL1 consensus sequence of X₁ASQGISX₂WLA (SEQ ID NO: 284), where X₁ is R or A; and X₂ is S or R. In another embodiment, the TREM2 agonist antigen binding proteins comprise a CDRL2 consensus sequence of X₁AX₂SLQN (SEQ ID NO: 285), where X₁ is A or S; and X₂ is S or G. In another embodiment, the TREM2 agonist antigen binding proteins comprise a CDRL3 consensus sequence of QQAX₁SFPX₂T (SEQ ID NO: 286), where X₁ is D or V; and X₂ is R or L. In

another embodiment, the TREM2 agonist antigen binding proteins comprise a CDRH1 consensus sequence of SX₁WIA (SEQ ID NO: 287), where X₁ is Y or E. In yet another embodiment, the TREM2 agonist antigen binding proteins comprise a CDRH2 consensus sequence of IYYPX₁DS DTRYSPSFQG (SEQ ID NO: 288), where X₁ is G or S. In still another embodiment, the TREM2 agonist antigen binding proteins comprise a CDRH3 consensus sequence of QRX₁FX₂X₃DSSDYFDY (SEQ ID NO: 289), where X₁ is T or G; X₂ is Y or R; and X₃ is Y or G. In certain embodiments, the TREM2 agonist antigen binding proteins comprise a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3 and a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3, wherein CDRL1 comprises the sequence of SEQ ID NO: 284, CDRL2 comprises the consensus sequence of SEQ ID NO: 285, CDRL3 comprises the consensus sequence of SEQ ID NO: 286, CDRH1 comprises the sequence of SEQ ID NO: 287, CDRH2 comprises the consensus sequence of SEQ ID NO: 288, and CDRH3 comprises the consensus sequence of SEQ ID NO: 289.

[0136] In some embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a CDRL1 comprising a sequence selected from SEQ ID NOs: 16, 290, and 291; a CDRL2 comprising a sequence selected from SEQ ID NOs: 28, 292, and 293; a CDRL3 comprising a sequence selected from SEQ ID NOs: 43, 294, and 271; a CDRH1 comprising the sequence of SEQ ID NO: 85 or SEQ ID NO: 302; a CDRH2 comprising the sequence of SEQ ID NO: 91 or SEQ ID NO: 303; and a CDRH3 comprising a sequence selected from SEQ ID NOs: 107 and 304-306.

[0137] In particular embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region comprising a CDRL1, a CDRL2, and a CDRL3, wherein: (a) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 28, and 43, respectively; (b) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 292, and 43, respectively; (c) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 28, and 294, respectively; (d) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 290, 28, and 43, respectively; (e) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 293, and 43, respectively; (f) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 28, and 271, respectively; or (g) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 291, 28, and 43, respectively.

[0138] In related embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a heavy chain variable region comprising a CDRH1, a CDRH2, and a CDRH3,

wherein: (a) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 91, and 304, respectively; (b) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 91, and 107, respectively; (c) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 91, and 305, respectively; (d) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 303, and 107, respectively; (e) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 91, and 306, respectively; or (f) CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 302, 91, and 107, respectively.

[0139] In certain embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain variable region comprising a CDRL1, a CDRL2, and a CDRL3 and a heavy chain variable region comprising a CDRH1, a CDRH2, and a CDRH3, wherein:

(a) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 28, and 43, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 91, and 304, respectively;

(b) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 292, and 43, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 91, and 107, respectively;

(c) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 28, and 294, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 91, and 107, respectively;

(d) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 28, and 43, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 91, and 107, respectively;

(e) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 28, and 43, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 91, and 305, respectively;

(f) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 28, and 43, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 303, and 107, respectively;

(g) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 290, 28, and 43, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 91, and 107, respectively;

(h) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 28, and 43, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 91, and 306, respectively;

(i) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 293, and 43, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 91, and 107, respectively;

(j) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 16, 28, and 271, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 85, 91, and 107, respectively; or

(k) CDRL1, CDRL2, and CDRL3 have the sequence of SEQ ID NOs: 291, 28, and 43, respectively, and CDRH1, CDRH2, and CDRH3 have the sequence of SEQ ID NOs: 302, 91, and 107, respectively.

[0140] In some embodiments, the TREM2 agonist antigen binding proteins of the invention may comprise a light chain variable region selected from LV-16, LV-201, LV-202, LV-203, LV-204, LV-205, and LV-206, as shown in Table 3A, and/or a heavy chain variable region selected from HV-15, HV-201, HV-202, HV-203, HV-204, HV-205, and HV-206, as shown in Table 3B, or sequences that are at least 80% identical, at least 85% identical, at least 90% identical, or at least 95% identical to any of the sequences in Tables 3A and 3B. For instance, in certain embodiments, the TREM2 agonist antigen binding proteins comprise a light chain variable region comprising (i) a sequence that is at least 90% identical to a sequence selected from SEQ ID NOs: 61 and 295-300, (ii) a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 61 and 295-300, or (iii) a sequence selected from SEQ ID NOs: 61 and 295-300. In related embodiments, the TREM2 agonist antigen binding proteins comprise a heavy chain variable region comprising (i) a sequence that is at least 90% identical to a sequence selected from SEQ ID NOs: 124 and 307-312, (ii) a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 124 and 307-312, or (iii) a sequence selected from SEQ ID NOs: 124 and 307-312.

[0141] Each of the light chain variable regions listed in Table 3A may be combined with any of the heavy chain variable regions listed in Table 3B to form an anti-TREM2 binding domain of the antigen binding proteins of the invention. Examples of such combinations include, but are not limited to: LV-16 (SEQ ID NO: 61) and HV-201 (SEQ ID NO: 307); LV-201 (SEQ ID NO: 295) and HV-15 (SEQ ID NO: 124); LV-202 (SEQ ID NO: 296) and HV-15 (SEQ ID NO: 124); LV-16 (SEQ ID NO: 61) and HV-202 (SEQ ID NO: 308); LV-16

(SEQ ID NO: 61) and HV-203 (SEQ ID NO: 309); LV-16 (SEQ ID NO: 61) and HV-204 (SEQ ID NO: 310); LV-203 (SEQ ID NO: 297) and HV-15 (SEQ ID NO: 124); LV-16 (SEQ ID NO: 61) and HV-205 (SEQ ID NO: 311); LV-204 (SEQ ID NO: 298) and HV-15 (SEQ ID NO: 124); LV-205 (SEQ ID NO: 299) and HV-15 (SEQ ID NO: 124); and LV-206 (SEQ ID NO: 300) and HV-206 (SEQ ID NO: 312).

[0142] In certain embodiments, the TREM2 agonist antigen binding proteins of the invention are anti-TREM2 agonist antibodies or binding fragments thereof. As used herein, the term “antibody” refers to a tetrameric immunoglobulin protein comprising two light chain polypeptides (about 25 kDa each) and two heavy chain polypeptides (about 50-70 kDa each). An “antibody” is a species of an antigen binding protein. The term “light chain” or “immunoglobulin light chain” refers to a polypeptide comprising, from amino terminus to carboxyl terminus, a single immunoglobulin light chain variable region (VL) and a single immunoglobulin light chain constant domain (CL). The immunoglobulin light chain constant domain (CL) can be a human kappa (κ) or human lambda (λ) constant domain. The term “heavy chain” or “immunoglobulin heavy chain” refers to a polypeptide comprising, from amino terminus to carboxyl terminus, a single immunoglobulin heavy chain variable region (VH), an immunoglobulin heavy chain constant domain 1 (CH1), an immunoglobulin hinge region, an immunoglobulin heavy chain constant domain 2 (CH2), an immunoglobulin heavy chain constant domain 3 (CH3), and optionally an immunoglobulin heavy chain constant domain 4 (CH4). Heavy chains are classified as mu (μ), delta (Δ), gamma (γ), alpha (α), and epsilon (ϵ), and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. The IgG-class and IgA-class antibodies are further divided into subclasses, namely, IgG1, IgG2, IgG3, and IgG4, and IgA1 and IgA2, respectively. The heavy chains in IgG, IgA, and IgD antibodies have three domains (CH1, CH2, and CH3), whereas the heavy chains in IgM and IgE antibodies have four domains (CH1, CH2, CH3, and CH4). The immunoglobulin heavy chain constant domains can be from any immunoglobulin isotype, including subtypes. The antibody chains are linked together via inter-polypeptide disulfide bonds between the CL domain and the CH1 domain (i.e. between the light and heavy chain) and between the hinge regions of the antibody heavy chains.

[0143] The anti-TREM2 antibodies of the invention can comprise any immunoglobulin constant region. The term “constant region” as used herein refers to all domains of an antibody other than the variable region. The constant region is not involved directly in binding of an antigen, but exhibits various effector functions. As described above, antibodies

are divided into particular isotypes (IgA, IgD, IgE, IgG, and IgM) and subtypes (IgG1, IgG2, IgG3, IgG4, IgA1 IgA2) depending on the amino acid sequence of the constant region of their heavy chains. The light chain constant region can be, for example, a kappa- or lambda-type light chain constant region, e.g., a human kappa- or lambda-type light chain constant region, which are found in all five antibody isotypes. Examples of human immunoglobulin light chain constant region sequences are shown in the following table.

Table 4. Exemplary Human Immunoglobulin Light Chain Constant Regions

Designation	SEQ ID NO:	CL Domain Amino Acid Sequence
Human lambda v1	191	GQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS
Human lambda v2	192	GQPKAAPSVTFLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQ VTHEGSTVEKTVAPTECS
Human lambda v3	193	QPKAAPSVTFLFPPSSEELQANKATLVCLISDFYPGAVTVAWKAD SSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQV THEGSTVEKTVAPTECS
Human lambda v4	194	GQPKAAPSVTFLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQ VTHEGSTVEKTVAPTECS
Human lambda v5	195	GQPKAAPSVTFLFPPSSEELQANKATLVCLVSDFYPGAVTVAWK ADGSPVKVGVEETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYS CRVTHEGSTVEKTVAPAECS
Human kappa v1	196	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEV THQGLSSPVTKSFNRGEC
Human kappa v2	197	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC

[0144] The heavy chain constant region of the anti-TREM2 antibodies of the invention can be, for example, an alpha-, delta-, epsilon-, gamma-, or mu-type heavy chain constant region, e.g., a human alpha-, delta-, epsilon-, gamma-, or mu-type heavy chain constant region. In some embodiments, the anti-TREM2 antibodies comprise a heavy chain constant region from an IgG1, IgG2, IgG3, or IgG4 immunoglobulin. In one embodiment, the anti-TREM2 antibody comprises a heavy chain constant region from a human IgG1 immunoglobulin. In such embodiments, the human IgG1 immunoglobulin constant region may comprise one or more mutations to prevent glycosylation of the antibody as described in more detail herein. In

another embodiment, the anti-TREM2 antibody comprises a heavy chain constant region from a human IgG2 immunoglobulin. In yet another embodiment, the anti-TREM2 antibody comprises a heavy chain constant region from a human IgG4 immunoglobulin. Examples of human IgG1, IgG2, and IgG4 heavy chain constant region sequences are shown below in Table 5.

Table 5. Exemplary Human Immunoglobulin Heavy Chain Constant Regions

Ig isotype	SEQ ID NO:	Heavy Chain Constant Region Amino Acid Sequence
Human IgG1z	198	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Human IgG1za	199	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Human IgG1f	200	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Human IgG1fa	201	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Human IgG1z aglycosylated v1	202	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA

Ig isotype	SEQ ID NO:	Heavy Chain Constant Region Amino Acid Sequence
		KTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Human IgG1z aglycosylated v2	203	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNA KTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Human IgG2	204	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVD HKPSNTKVDKTVKCCVECPAPPVAGPSVFLFPPKPKDT LMISRTPEVTCVVDVSHEDPEVQFNWYVDGVEVHNAKTKP REEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIE KTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK
Human IgG4	205	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNA KTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[0145] Each of the light chain variable regions disclosed in Tables 1A, 2A, and 3A and each of the heavy chain variable regions disclosed in Tables 1B, 2B, and 3B may be attached to the above light chain constant regions (Table 4) and heavy chain constant regions (Table 5) to form complete antibody light and heavy chains, respectively. Further, each of the so generated heavy and light chain sequences may be combined to form a complete antibody structure. It should be understood that the heavy chain and light chain variable regions provided herein can also be attached to other constant domains having different sequences than the exemplary sequences listed above.

[0146] The TREM2 agonist antigen binding proteins of the invention can be any of the anti-TREM2 antibodies disclosed herein. For example, in certain embodiments, the anti-TREM2 agonist antigen binding protein is an anti-TREM2 antibody selected from antibodies 12G10, 26A10, 26C10, 26F2, 33B12, 24C12, 24G6, 24A10, 10E3, 13E7, 14C12, 25F12, 32E3, 24F4,

16B8, 4C5, 6E7, 5E3, and 4G10, the variable region and CDR sequences of which are set forth in Tables 1A and 1B. In some embodiments, the anti-TREM2 agonist antigen binding protein is an anti-TREM2 antibody selected from antibodies 24G6, 10E3, 13E7, 4C5, 6E7, and 5E3. In other embodiments, the anti-TREM2 agonist antigen binding protein is an anti-TREM2 antibody selected from antibodies V3, V24, V27, V40, V48, V49, V52, V60, V73, V76, and V84, the variable region and CDR sequences of which are set forth in Tables 2A and 2B. In certain other embodiments, the anti-TREM2 agonist antigen binding protein is an anti-TREM2 antibody selected from antibodies V9, V10, V23, V30, V33, V44, V57, V68, V70, V83, and V90, the variable region and CDR sequences of which are set forth in Tables 3A and 3B.

[0147] The TREM2 agonist antigen binding proteins of the invention can be monoclonal antibodies, polyclonal antibodies, recombinant antibodies, human antibodies, humanized antibodies, chimeric antibodies, or multispecific antibodies. In certain embodiments, the TREM2 agonist antigen binding protein is a monoclonal antibody. In such embodiments, the anti-TREM2 antibody may be a chimeric antibody, a humanized antibody, or a fully human antibody having a human immunoglobulin constant domain. In these and other embodiments, the anti-TREM2 antibody is a human IgG1, IgG2, IgG3, or IgG4 antibody. Thus, the anti-TREM2 antibody may, in some embodiments, have a human IgG1, IgG2, IgG3, or IgG4 constant domain. In one embodiment, the anti-TREM2 antibody is a monoclonal human IgG1 antibody. In another embodiment, the anti-TREM2 antibody is a monoclonal human IgG2 antibody. In yet another embodiment, the anti-TREM2 antibody is a monoclonal human IgG4 antibody.

[0148] The term “monoclonal antibody” (or “mAb”) as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against an individual antigenic site or epitope, in contrast to polyclonal antibody preparations that typically include different antibodies directed against different epitopes. Monoclonal antibodies may be produced using any technique known in the art, e.g., by immortalizing spleen cells harvested from an animal after completion of the immunization schedule. The spleen cells can be immortalized using any technique known in the art, e.g., by fusing them with myeloma cells to produce hybridomas. See, for example, *Antibodies*; Harlow and Lane, Cold Spring Harbor Laboratory Press, 1st Edition, e.g. from 1988, or 2nd

Edition, e.g. from 2014. Myeloma cells for use in hybridoma-producing fusion procedures preferably are non-antibody-producing, have high fusion efficiency, and enzyme deficiencies that render them incapable of growing in certain selective media, which support the growth of only the desired fused cells (hybridomas). Examples of suitable cell lines for use in fusions with mouse cells include, but are not limited to, Sp-20, P3-X63/Ag8, P3-X63-Ag8.653, NS1/1.Ag 4 1, Sp210-Ag14, FO, NSO/U, MPC-11, MPC11-X45-GTG 1.7 and S194/5XXO Bul. Example of suitable cell lines used for fusions with rat cells include, but are not limited to, R210.RCY3, Y3-Ag 1.2.3, IR983F and 4B210. Other cell lines useful for cell fusions are U-266, GM1500-GRG2, LICR-LON-HMy2 and UC729-6.

[0149] In some instances, a hybridoma cell line is produced by immunizing an animal (e.g., a rabbit, rat, mouse, or a transgenic animal having human immunoglobulin sequences) with a TREM2 immunogen (such as the immunogens described in Example 1); harvesting spleen cells from the immunized animal; fusing the harvested spleen cells to a myeloma cell line, thereby generating hybridoma cells; establishing hybridoma cell lines from the hybridoma cells, and identifying a hybridoma cell line that produces an antibody that binds to human TREM2. Another useful method for producing monoclonal antibodies is the SLAM method described in Babcock *et al.*, Proc. Natl. Acad. Sci. USA, Vol. 93: 7843-7848, 1996.

[0150] Monoclonal antibodies secreted by a hybridoma cell line can be purified using any technique known in the art, such as protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography. Hybridoma supernatants or mAbs may be further screened to identify mAbs with particular properties, such as the ability to bind human TREM2, cross-reactivity to TREM2 proteins from other species (e.g., mouse TREM2, rat TREM2, and cynomolgus monkey TREM2), cross-reactivity to other TREM family members (e.g. human TREM1), ability to induce or increase TREM2-mediated signaling, e.g. using a pSyk assay as described herein, or ability to induce or increase TREM2-mediated function or activities as described herein (e.g. proliferation or survival of TREM2-expressing myeloid cells).

[0151] In some embodiments, the TREM2 agonist antigen binding proteins of the invention are chimeric or humanized antibodies based upon the CDR and variable region sequences of the anti-TREM2 antibodies described herein. A chimeric antibody is an antibody composed of protein segments from different antibodies that are covalently joined to produce functional immunoglobulin light or heavy chains or binding fragments thereof. Generally, a portion of the heavy chain and/or light chain is identical with or homologous to a corresponding

sequence in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is/are identical with or homologous to a corresponding sequence in antibodies derived from another species or belonging to another antibody class or subclass. For methods relating to chimeric antibodies, see, for example, United States Patent No. 4,816,567 and Morrison *et al.*, 1985, Proc. Natl. Acad. Sci. USA 81:6851-6855, both of which are hereby incorporated by reference in their entireties.

[0152] Generally, the goal of making a chimeric antibody is to create a chimera in which the number of amino acids from the intended species is maximized. One example is the “CDR-grafted” antibody, in which the antibody comprises one or more CDRs from a particular species or belonging to a particular antibody class or subclass, while the remainder of the antibody chain(s) is/are identical with or homologous to a corresponding sequence in antibodies derived from another species or belonging to another antibody class or subclass. CDR grafting is described, for example, in United States Patent No. 6,180,370, No. 5,693,762, No. 5,693,761, No. 5,585,089, and No. 5,530,101. For use in humans, the variable region or selected CDRs from a rodent or rabbit antibody often are grafted into a human antibody, replacing the naturally-occurring variable regions or CDRs of the human antibody.

[0153] One useful type of chimeric antibody is a “humanized” antibody. Generally, a humanized antibody is produced from a monoclonal antibody raised initially in a non-human animal, such as a rodent or rabbit. Certain amino acid residues in this monoclonal antibody, typically from non-antigen recognizing portions of the antibody, are modified to be homologous to corresponding residues in a human antibody of corresponding isotype. Humanization can be performed, for example, using various methods by substituting at least a portion of a rodent or rabbit variable region for the corresponding regions of a human antibody (see, e.g., United States Patent No. 5,585,089, and No. 5,693,762; Jones *et al.*, 1986, Nature 321:522-525; Riechmann *et al.*, 1988, Nature 332:323-27; and Verhoeven *et al.*, 1988, Science 239:1534-1536).

[0154] In one aspect, the CDRs of the light and heavy chain variable regions of the antibodies provided herein (see, Tables 1A, 1B, 2A, 2B, 3A and 3B) are grafted to framework regions (FRs) from antibodies from the same, or a different, phylogenetic species. For example, the CDRs of the heavy and light chain variable regions listed in Tables 1A, 1B, 2A, 2B, 3A, and 3B can be grafted to consensus human FRs. To create consensus human FRs, FRs from several human heavy chain or light chain amino acid sequences may be aligned to

identify a consensus amino acid sequence. Alternatively, the grafted variable regions from the one heavy or light chain may be used with a constant region that is different from the constant region of that particular heavy or light chain as disclosed herein. In other embodiments, the grafted variable regions are part of a single chain Fv antibody.

[0155] In certain embodiments, the TREM2 agonist antigen binding proteins of the invention are fully human antibodies. Fully human antibodies that specifically bind to human TREM2 can be generated using the immunogens or fragments thereof described herein, such as polypeptides consisting of the sequences of SEQ ID NOs: 1 and 2 or the immunogens described in Example 1. A “fully human antibody” is an antibody that comprises variable and constant regions derived from or indicative of human germ line immunoglobulin sequences. One specific means provided for implementing the production of fully human antibodies is the “humanization” of the mouse humoral immune system. Introduction of human immunoglobulin (Ig) loci into mice in which the endogenous Ig genes have been inactivated is one means of producing fully human monoclonal antibodies (mAbs) in mouse, an animal that can be immunized with any desirable antigen. Using fully human antibodies can minimize the immunogenic and allergic responses that can sometimes be caused by administering mouse or mouse-derived mAbs to humans as therapeutic agents.

[0156] Fully human antibodies can be produced by immunizing transgenic animals (usually mice) that are capable of producing a repertoire of human antibodies in the absence of endogenous immunoglobulin production. Antigens for this purpose typically have six or more contiguous amino acids, and optionally are conjugated to a carrier, such as a hapten. *See, e.g., Jakobovits et al., 1993, Proc. Natl. Acad. Sci. USA 90:2551-2555; Jakobovits et al., 1993, Nature 362:255-258; and Bruggermann et al., 1993, Year in Immunol. 7:33.* In one example of such a method, transgenic animals are produced by incapacitating the endogenous mouse immunoglobulin loci encoding the mouse heavy and light immunoglobulin chains therein, and inserting into the mouse genome large fragments of human genome DNA containing loci that encode human heavy and light chain proteins. Partially modified animals, which have less than the full complement of human immunoglobulin loci, are then cross-bred to obtain an animal having all of the desired immune system modifications. When administered an immunogen, these transgenic animals produce antibodies that are immunospecific for the immunogen but have human rather than murine amino acid sequences, including the variable regions. For further details of such methods, *see, for example, WO96/33735 and WO94/02602.* Additional methods relating to transgenic mice

for making human antibodies are described in United States Patent No. 5,545,807; No. 6,713,610; No. 6,673,986; No. 6,162,963; No. 5,939,598; No. 5,545,807; No. 6,300,129; No. 6,255,458; No. 5,877,397; No. 5,874,299 and No. 5,545,806; in PCT publications WO91/10741, WO90/04036, WO 94/02602, WO 96/30498, WO 98/24893 and in EP 546073B1 and EP 546073A1.

[0157] The transgenic mice described above, referred to herein as “HuMab” mice, contain a human immunoglobulin gene minilocus that encodes unrearranged human heavy (mu and gamma) and kappa light chain immunoglobulin sequences, together with targeted mutations that inactivate the endogenous mu and kappa chain loci (Lonberg *et al.*, 1994, *Nature* 368:856-859). Accordingly, the mice exhibit reduced expression of mouse IgM and kappa proteins and in response to immunization, the introduced human heavy and light chain transgenes undergo class switching and somatic mutation to generate high affinity human IgG kappa monoclonal antibodies (Lonberg and Huszar, 1995, *Intern. Rev. Immunol.* 13: 65-93; Harding and Lonberg, 1995, *Ann. N.Y Acad. Sci.* 764:536-546). The preparation of HuMab mice is described in detail in Taylor *et al.*, 1992, *Nucleic Acids Research* 20:6287-6295; Chen *et al.*, 1993, *International Immunology* 5:647-656; Tuaillon *et al.*, 1994, *J. Immunol.* 152:2912-2920; Lonberg *et al.*, 1994, *Nature* 368:856-859; Lonberg, 1994, *Handbook of Exp. Pharmacology* 113:49-101; Taylor *et al.*, 1994, *International Immunology* 6:579-591; Lonberg and Huszar, 1995, *Intern. Rev. Immunol.* 13:65-93; Harding and Lonberg, 1995, *Ann. N.Y Acad. Sci.* 764:536-546; Fishwild *et al.*, 1996, *Nature Biotechnology* 14:845-851; the foregoing references are hereby incorporated by reference in their entireties for all purposes. See, further United States Patent No. 5,545,806; No. 5,569,825; No. 5,625,126; No. 5,633,425; No. 5,789,650; No. 5,877,397; No. 5,661,016; No. 5,814,318; No. 5,874,299; and No. 5,770,429; as well as United States Patent No. 5,545,807; International Publication Nos. WO 93/1227; WO 92/22646; and WO 92/03918, the disclosures of all of which are hereby incorporated by reference in their entireties for all purposes. Technologies utilized for producing human antibodies in these transgenic mice are disclosed also in WO 98/24893, and Mendez *et al.*, 1997, *Nature Genetics* 15:146-156, which are hereby incorporated by reference. For example, the HCo7 and HCo12 transgenic mice strains can be used to generate fully human anti-TREM2 antibodies. One particular transgenic mouse line suitable for generation of fully human anti-TREM antibodies is the XenoMouse® transgenic mice described in Example 1 and in U.S. Pat. Nos. 6,114,598; 6,162,963; 6,833,268; 7,049,426; 7,064,244; Green *et al.*, 1994, *Nature Genetics* 7:13-21; Mendez *et al.*, 1997, *Nature*

Genetics 15:146-156; Green and Jakobovitis, 1998, *J. Ex. Med.*, 188:483-495; Green, 1999, *Journal of Immunological Methods* 231:11-23; Kellerman and Green, *Current Opinion in Biotechnology* 13, 593-597, 2002, all of which are hereby incorporated by reference in their entireties.

[0158] Human-derived antibodies can also be generated using phage display techniques. Phage display is described in e.g., Dower *et al.*, WO 91/17271, McCafferty *et al.*, WO 92/01047, and Caton and Koprowski, *Proc. Natl. Acad. Sci. USA*, 87:6450-6454 (1990), each of which is incorporated herein by reference in its entirety. The antibodies produced by phage technology are usually produced as antigen binding fragments, e.g. Fv or Fab fragments, in bacteria and thus lack effector functions. Effector functions can be introduced by one of two strategies: The fragments can be engineered either into complete antibodies for expression in mammalian cells, or into bispecific antibody fragments with a second binding site capable of triggering an effector function, if desired. Typically, the Fd fragment (VH-CH1) and light chain (VL-CL) of antibodies are separately cloned by PCR and recombined randomly in combinatorial phage display libraries, which can then be selected for binding to a particular antigen. The antibody fragments are expressed on the phage surface, and selection of Fv or Fab (and therefore the phage containing the DNA encoding the antibody fragment) by antigen binding is accomplished through several rounds of antigen binding and re-amplification, a procedure termed panning. Antibody fragments specific for the antigen are enriched and finally isolated. Phage display techniques can also be used in an approach for the humanization of rodent monoclonal antibodies, called "guided selection" (*see* Jespers, L. S., *et al.*, *Bio/Technology* 12, 899-903 (1994)). For this, the Fd fragment of the mouse monoclonal antibody can be displayed in combination with a human light chain library, and the resulting hybrid Fab library may then be selected with antigen. The mouse Fd fragment thereby provides a template to guide the selection. Subsequently, the selected human light chains are combined with a human Fd fragment library. Selection of the resulting library yields entirely human Fab.

[0159] Once cells producing anti-TREM2 antibodies according to the invention have been obtained using any of the above-described immunization and other techniques, the specific antibody genes may be cloned by isolating and amplifying DNA or mRNA therefrom according to standard procedures as described herein. The antibodies produced therefrom may be sequenced and the CDRs identified and the DNA coding for the CDRs may be

manipulated as described herein to generate other TREM2 agonist antigen binding proteins or antibodies according to the invention.

[0160] In certain embodiments, the TREM2 agonist antigen binding proteins of the invention (e.g. monoclonal antibodies or binding fragments thereof) compete for binding to human TREM2 (SEQ ID NO: 1) or an extracellular domain of human TREM2 (SEQ ID NO: 2) with a reference antibody, such as one or more of the anti-TREM2 antibodies described herein. The term “compete” refers to the ability of an antibody or other antigen binding protein to interfere with the binding of other antibodies or binding fragments to a target (e.g. human TREM2). The extent to which an antibody or binding fragment is able to interfere with the binding of another antibody or binding fragment to a target (e.g. human TREM2), and therefore whether it can be said to compete, can be determined using competition binding assays. Numerous types of competitive binding assays can be used, including for example: solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (*see, e.g.,* Stahl *et al.*, 1983, *Methods in Enzymology* 9:242-253); solid phase direct biotin-avidin EIA (*see, e.g.,* Kirkland *et al.*, 1986, *J. Immunol.* 137:3614-3619); solid phase direct-labeled assay, solid phase direct-labeled sandwich assay (*see, e.g.,* Harlow and Lane, 1988, *Antibodies, A Laboratory Manual*, Cold Spring Harbor Press); solid phase direct label RIA using I-125 label (*see, e.g.,* Morel *et al.*, 1988, *Molec. Immunol.* 25:7-15); solid phase direct biotin-avidin EIA (*see, e.g.,* Cheung, *et al.*, 1990, *Virology* 176:546-552); surface plasmon resonance-based assays (e.g. using Biacore® systems); bio-layer interferometry-based assays (e.g. using Octet® systems); and direct labeled RIA (Moldenhauer *et al.*, 1990, *Scand. J. Immunol.* 32:77-82). Typically, a competitive binding assay involves the use of purified antigen bound to a solid surface or cells bearing the antigen, an unlabeled test antibody or other antigen binding protein, and a labeled reference antibody or other antigen binding protein. Competitive inhibition is measured by determining the amount of label bound to the solid surface or cells in the presence of the test antibody or other antigen binding protein. Usually the test antibody or other antigen binding protein is present in excess. Antibodies or other antigen binding proteins identified by competition assay (i.e. competing antibodies and antigen binding proteins) include antibodies and antigen binding proteins binding to the same epitope as the reference antibody or antigen binding protein. Usually, when a competing antibody or other antigen binding protein is present in excess, it will inhibit specific binding of a reference antibody or other antigen binding protein to a target antigen by at least 40%, 45%, 50%, 55%,

60%, 65%, 70% or 75%. In some instances, binding of the reference antibody or other antigen binding protein is inhibited by at least 80%, 85%, 90%, 95%, or 97% or more. In some embodiments, a competing antigen binding protein (e.g. antibody or binding fragment thereof) reduces human TREM2 binding of a reference antibody between about 40% and about 100%, such as about 60% and about 100%, specifically between about 70% and about 100%, and more specifically between about 80% and about 100%.

[0161] A particularly suitable quantitative assay for detecting competitive binding uses a Biacore[®] machine which measures the extent of interactions using surface plasmon resonance technology. An exemplary Biacore[®]-based competitive binding assay involves the immobilization of a reference antibody to a sensor chip. The target antigen is then contacted with the sensor chip where the target antigen is captured by the immobilized reference antibody. Test antibodies are then injected over the captured target antigen. If the injected test antibody recognizes a distinct epitope from that recognized by the immobilized antibody, then a second binding event is observed and the test antibody would be considered not to compete for binding to the target antigen with the reference antibody.

[0162] Another particularly suitable assay for detecting competitive binding employs kinetic sensors used with Octet[®] systems (Pall ForteBio), which measures binding interactions using bio-layer interferometry methodology. Such an assay is described in Example 4, in which each of sixteen different anti-TREM2 antibodies described herein were evaluated against each other for the ability to compete for binding to human TREM2. The results of the analysis provided in Table 9 show that the sixteen different antibodies could be grouped into four distinct epitope bins. That is, one group of antibodies (antibodies 10E3, 13E7, 24F4, 4C5, 4G10, 32E3, and 6E7) competed with each other for binding to human TREM2, indicating that they share the same or similar epitope on human TREM2. Antibodies 16B8, 26A10, 26C10, 26F2, 33B12, and 5E3 competed with each other for TREM2 binding, but did not compete with antibodies in the first group or antibodies 24A10, 24G6, or 25F12, indicating that this second group of antibodies bind to a distinct epitope on human TREM2. Antibodies 24A10 and 24G6 share a similar epitope on human TREM2 as these two antibodies competed with each other for human TREM2 binding, but did not compete with any other antibody. Antibody 25F12 did not compete with any of the other tested antibodies for human TREM2 binding, indicating that this antibody binds to yet another epitope.

[0163] In some embodiments, a TREM2 agonist antigen binding protein of the invention competes with a reference antibody for binding to human TREM2, wherein the reference

antibody comprises a light chain variable region comprising a sequence selected from SEQ ID NOs: 46-63 and a heavy chain variable region comprising a sequence selected from SEQ ID NOs: 110-126. In other embodiments, a TREM2 agonist antigen binding protein of the invention competes with a reference antibody for binding to human TREM2, wherein the reference antibody comprises a light chain variable region comprising a sequence selected from SEQ ID NOs: 153-162 and a heavy chain variable region comprising a sequence selected from SEQ ID NOs: 180-190. In still other embodiments, a TREM2 agonist antigen binding protein of the invention competes with a reference antibody for binding to human TREM2, wherein the reference antibody comprises a light chain variable region comprising a sequence selected from SEQ ID NOs: 61 and 295-300 and a heavy chain variable region comprising a sequence selected from SEQ ID NOs: 124 and 307-312. In certain embodiments, a TREM2 agonist antigen binding protein of the invention competes for binding to human TREM2 with one or more of the anti-TREM2 antibodies described herein, including 12G10, 26A10, 26C10, 26F2, 33B12, 24C12, 24G6, 24A10, 10E3, 13E7, 14C12, 25F12, 32E3, 24F4, 16B8, 4C5, 6E7, 5E3, 4G10, V3, V9, V10, V23, V24, V27, V30, V33, V40, V44, V48, V49, V52, V57, V60, V68, V70, V73, V76, V83, V84, and V90.

[0164] In one embodiment, the TREM2 agonist antigen binding protein competes with a reference antibody for binding to human TREM2, wherein the reference antibody comprises a light chain variable region comprising the sequence of SEQ ID NO: 61 and a heavy chain variable region comprising the sequence of SEQ ID NO: 124. In such embodiments, antigen binding proteins that compete with this reference antibody for binding to human TREM2 would bind the same or similar epitope as antibody 6E7 or any of the other antibodies in epitope bin A (e.g. 10E3, 13E7, 24F4, 4C5, 4G10, 32E3), as described in Example 4.

[0165] In another embodiment, the TREM2 agonist antigen binding protein competes with a reference antibody for binding to human TREM2, wherein the reference antibody comprises a light chain variable region comprising the sequence of SEQ ID NO: 62 and a heavy chain variable region comprising the sequence of SEQ ID NO: 125. In such embodiments, antigen binding proteins that compete with this reference antibody for binding to human TREM2 would bind the same or similar epitope as antibody 5E3 or any of the other antibodies in epitope bin B (e.g. 16B8, 26A10, 26C10, 26F2, 33B12), as described in Example 4.

[0166] In yet another embodiment, the TREM2 agonist antigen binding protein competes with a reference antibody for binding to human TREM2, wherein the reference antibody comprises a light chain variable region comprising the sequence of SEQ ID NO: 52 and a

heavy chain variable region comprising the sequence of SEQ ID NO: 115. In such embodiments, antigen binding proteins that compete with this reference antibody for binding to human TREM2 would bind the same or similar epitope as antibody 24G6 or antibody 24A10 (epitope bin C as described in Example 4).

[0167] In still another embodiment, the TREM2 agonist antigen binding protein competes with a reference antibody for binding to human TREM2, wherein the reference antibody comprises a light chain variable region comprising the sequence of SEQ ID NO: 56 and a heavy chain variable region comprising the sequence of SEQ ID NO: 119. In such embodiments, antigen binding proteins that compete with this reference antibody for binding to human TREM2 would bind the same or similar epitope as antibody 25F12 (epitope bin D as described in Example 4).

[0168] In certain embodiments, the TREM2 agonist antigen binding proteins of the invention may comprise one or more mutations or modifications to a constant region. For example, in embodiments in which the TREM2 agonist antigen binding proteins comprise an Fc region (e.g. monoclonal antibodies), the heavy chain constant regions or the Fc regions of the antigen binding proteins (e.g. monoclonal antibodies) may comprise one or more amino acid substitutions that affect the glycosylation, effector function, and/or Fcγ receptor binding of the antigen binding protein.

[0169] The term “Fc region” refers to the C-terminal region of an immunoglobulin heavy chain which may be generated by papain digestion of an intact antibody. The Fc region of an immunoglobulin generally comprises two constant domains, a CH2 domain and a CH3 domain, and optionally comprises a CH4 domain. In certain embodiments, the Fc region is an Fc region from an IgG1, IgG2, IgG3, or IgG4 immunoglobulin. In some embodiments, the Fc region comprises CH2 and CH3 domains from a human IgG1 or human IgG2 immunoglobulin. The Fc region may retain effector function, such as C1q binding, complement-dependent cytotoxicity (CDC), Fc receptor binding, antibody-dependent cell-mediated cytotoxicity (ADCC), and phagocytosis. In other embodiments, the Fc region may be modified to reduce or eliminate effector function as described in further detail below.

[0170] One of the functions of the Fc region of an immunoglobulin is to communicate to the immune system when the immunoglobulin binds its target. This is commonly referred to as “effector function.” Communication leads ADCC, antibody-dependent cellular phagocytosis (ADCP), and/or CDC. ADCC and ADCP are mediated through the binding of the Fc region to Fc receptors on the surface of cells of the immune system. CDC is mediated through the

binding of the Fc with proteins of the complement system, e.g., C1q. In some embodiments, the antigen binding proteins, e.g. monoclonal antibodies, of the invention comprise one or more amino acid substitutions in the Fc region to enhance effector function, including ADCC activity, CDC activity, ADCP activity, and/or the clearance or half-life of the antigen binding protein. Exemplary amino acid substitutions (according to EU numbering scheme) that can enhance effector function include, but are not limited to, E233L, L234I, L234Y, L235S, G236A, S239D, F243L, F243V, P247I, D280H, K290S, K290E, K290N, K290Y, R292P, E294L, Y296W, S298A, S298D, S298V, S298G, S298T, T299A, Y300L, V305I, Q311M, K326A, K326E, K326W, A330S, A330L, A330M, A330F, I332E, D333A, E333S, E333A, K334A, K334V, A339D, A339Q, P396L, or combinations of any of the foregoing.

[0171] In other embodiments, the TREM2 agonist antigen binding proteins (e.g. monoclonal antibodies) of the invention comprise one or more amino acid substitutions in a heavy chain constant region to reduce effector function. Exemplary amino acid substitutions (according to EU numbering scheme) that can reduce effector function include, but are not limited to, C220S, C226S, C229S, E233P, L234A, L234V, V234A, L234F, L235A, L235E, G237A, P238S, S267E, H268Q, N297A, N297G, V309L, E318A, L328F, A330S, A331S, P331S or combinations of any of the foregoing.

[0172] Glycosylation can contribute to the effector function of antibodies, particularly IgG1 antibodies. Thus, in some embodiments, the TREM2 agonist antigen binding proteins of the invention may comprise one or more amino acid substitutions that affect the level or type of glycosylation of the binding proteins. Glycosylation of polypeptides is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tri-peptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tri-peptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-acetylgalactosamine, galactose, or xylose, to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used.

[0173] In certain embodiments, glycosylation of the TREM2 agonist antigen binding proteins described herein is increased by adding one or more glycosylation sites, e.g., to the Fc region of the binding protein. Addition of glycosylation sites to the antigen binding protein can be conveniently accomplished by altering the amino acid sequence such that it contains one or

more of the above-described tri-peptide sequences (for N-linked glycosylation sites). The alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues to the starting sequence (for O-linked glycosylation sites). For ease, the antigen binding protein amino acid sequence may be altered through changes at the DNA level, particularly by mutating the DNA encoding the target polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

[0174] The invention also encompasses production of TREM2 antigen binding protein molecules with altered carbohydrate structure resulting in altered effector activity, including antigen binding proteins with absent or reduced fucosylation that exhibit improved ADCC activity. Various methods are known in the art to reduce or eliminate fucosylation. For example, ADCC effector activity is mediated by binding of the antibody molecule to the FcγRIII receptor, which has been shown to be dependent on the carbohydrate structure of the N-linked glycosylation at the N297 residue of the CH2 domain. Non-fucosylated antibodies bind this receptor with increased affinity and trigger FcγRIII-mediated effector functions more efficiently than native, fucosylated antibodies. For example, recombinant production of non-fucosylated antibody in CHO cells in which the alpha-1,6-fucosyl transferase enzyme has been knocked out results in antibody with 100-fold increased ADCC activity (*see Yamane-Ohnuki et al.*, *Biotechnol Bioeng.* 87(5):614-22, 2004). Similar effects can be accomplished through decreasing the activity of alpha-1,6-fucosyl transferase enzyme or other enzymes in the fucosylation pathway, e.g., through siRNA or antisense RNA treatment, engineering cell lines to knockout the enzyme(s), or culturing with selective glycosylation inhibitors (*see Rothman et al.*, *Mol Immunol.* 26(12):1113-23, 1989). Some host cell strains, e.g. Lec13 or rat hybridoma YB2/0 cell line naturally produce antibodies with lower fucosylation levels (*see Shields et al.*, *J Biol Chem.* 277(30):26733-40, 2002 and Shinkawa *et al.*, *J Biol Chem.* 278(5):3466-73, 2003). An increase in the level of bisected carbohydrate, e.g. through recombinantly producing antibody in cells that overexpress GnTIII enzyme, has also been determined to increase ADCC activity (*see Umana et al.*, *Nat Biotechnol.* 17(2):176-80, 1999).

[0175] In other embodiments, glycosylation of the TREM2 agonist antigen binding proteins described herein is decreased or eliminated by removing one or more glycosylation sites, e.g., from the Fc region of the binding protein. In some embodiments, the TREM2 agonist antigen binding protein is an aglycosylated human monoclonal antibody, e.g. an aglycosylated human IgG1 monoclonal antibody. Amino acid substitutions that eliminate or alter N-linked

glycosylation sites can reduce or eliminate N-linked glycosylation of the antigen binding protein. In certain embodiments, the TREM2 agonist antigen binding proteins described herein comprise a mutation at position N297 (according to EU numbering scheme), such as N297Q, N297A, or N297G. In some embodiments, the TREM2 agonist antigen binding proteins of the invention comprise an Fc region from a human IgG1 antibody with a mutation at position N297. In one particular embodiment, the TREM2 agonist antigen binding proteins of the invention comprise an Fc region from a human IgG1 antibody with a N297G mutation. For instance, in some embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a heavy chain constant region comprising the sequence of SEQ ID NO: 202.

[0176] To improve the stability of molecules comprising a N297 mutation, the Fc region of the TREM2 agonist antigen binding proteins may be further engineered. For instance, in some embodiments, one or more amino acids in the Fc region are substituted with cysteine to promote disulfide bond formation in the dimeric state. Residues corresponding to V259, A287, R292, V302, L306, V323, or I332 (according to EU numbering scheme) of an IgG1 Fc region may thus be substituted with cysteine. Preferably, specific pairs of residues are substituted with cysteine such that they preferentially form a disulfide bond with each other, thus limiting or preventing disulfide bond scrambling. Preferred pairs include, but are not limited to, A287C and L306C, V259C and L306C, R292C and V302C, and V323C and I332C. In certain embodiments, the TREM2 agonist antigen binding proteins described herein comprise an Fc region from a human IgG1 antibody with mutations R292C and V302C. In such embodiments, the Fc region may also comprise a N297 mutation, such as a N297G mutation. In some embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a heavy chain constant region comprising the sequence of SEQ ID NO: 203.

[0177] Modifications to the hinge region and/or CH1 domain of the heavy chain and/or the constant region of the light chain of the TREM2 agonist antigen binding proteins (e.g. monoclonal antibodies) of the invention can be made to reduce or eliminate disulfide heterogeneity. Structural heterogeneity of IgG2 antibodies has been observed where the disulfide bonds in the hinge and CH1 regions of IgG2 antibodies can be shuffled to create different structural disulfide isoforms (IgG2A, IgG2B, and IgG2A-B), which can have different levels of activity. *See, e.g.*, Dillon *et al.*, J. Biol. Chem., Vol. 283: 16206-16215; Martinez *et al.*, Biochemistry, Vol. 47: 7496-7508, 2008; and White *et al.*, Cancer Cell, Vol.

27: 138-148, 2015. Amino acid substitutions can be made in the hinge region, CH1 domain, and/or light chain constant region to promote the formation of a single disulfide isoform or lock the antigen binding protein (e.g. monoclonal antibody) into a particular disulfide isoform (e.g. IgG2A or IgG2B). Such mutations are described in WO 2009/036209 and White *et al.*, Cancer Cell, Vol. 27: 138-148, 2015, both of which are hereby incorporated by reference in its entirety, and include C131S, C219S, and C220S (according to EU numbering scheme) mutations in the heavy chain and a C214S (according to EU numbering scheme) mutation in the light chain. In certain embodiments, the TREM2 agonist antigen binding proteins of the invention are human IgG2 anti-TREM2 agonist antibodies. In some such embodiments, the TREM2 agonist antibodies comprise a C131S mutation (according to the EU numbering scheme) in their heavy chains. In other embodiments, the TREM2 agonist antibodies comprise a C214S mutation (according to the EU numbering scheme) in their light chains and a C220S mutation (according to the EU numbering scheme) in their heavy chains. In still other embodiments, the TREM2 agonist antibodies comprise a C214S mutation (according to the EU numbering scheme) in their light chains and a C219S mutation (according to the EU numbering scheme) in their heavy chains.

[0178] In other embodiments, the TREM2 agonist antigen binding proteins of the invention are anti-TREM2 agonist antibodies comprising a CH1 region and hinge region from a human IgG2 antibody and an Fc region from a human IgG1 antibody. The unique arrangement of the disulfide bonds in the hinge region of IgG2 antibodies has been reported to impart enhanced stimulatory activity for certain anticancer antibodies (White *et al.*, Cancer Cell, Vol. 27: 138-148, 2015). This enhanced activity could be transferred to IgG1-type antibodies by exchanging the CH1 and hinge regions of the IgG1 antibody for those in the IgG2 antibody (White *et al.*, 2015). The IgG2 hinge region includes the amino acid sequence ERKCCVECPCP (SEQ ID NO: 206). The amino acid sequence of the CH1 and hinge regions from a human IgG2 antibody may comprise the amino acid sequence of ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSNFGTQT YTCNVDPKPS NTKVDKTVR KCCVECPCP (SEQ ID NO: 207). Thus, in some embodiments, the anti-TREM2 agonist antibodies comprise the sequence of SEQ ID NO: 207 in combination with an Fc region from a human IgG1 antibody. In such embodiments, the anti-TREM2 antibodies can comprise one or more of the mutations described above to lock the anti-TREM2 antibodies into a particular disulfide isoform. For instance, in one embodiment, the anti-TREM2 antibody comprises a

CH1 region and hinge region from a human IgG2 antibody and an Fc region from a human IgG1 antibody and comprises a C131S mutation (according to the EU numbering scheme) in its heavy chain. In another embodiment, the anti-TREM2 antibody comprises a CH1 region and hinge region from a human IgG2 antibody and an Fc region from a human IgG1 antibody and comprises a C214S mutation (according to the EU numbering scheme) in its light chain and a C220S mutation (according to the EU numbering scheme) in its heavy chain. In yet another embodiment, the anti-TREM2 antibody comprises a CH1 region and hinge region from a human IgG2 antibody and an Fc region from a human IgG1 antibody and comprises a C214S mutation (according to the EU numbering scheme) in its light chain and a C219S mutation (according to the EU numbering scheme) in its heavy chain.

[0179] In embodiments in which the anti-TREM2 antibodies comprise a CH1 region and hinge region from a human IgG2 antibody and an Fc region from a human IgG1 antibody, the anti-TREM2 antibodies may comprise any of the mutations in the Fc region described above to modulate the glycosylation of the antibodies. For instance, the human IgG1 Fc region of such anti-TREM2 antibodies may comprise a mutation at amino acid position N297 (according to the EU numbering scheme) in its heavy chain. In one particular embodiment, the N297 mutation is a N297G mutation. In certain embodiments, the Fc region may further comprise R292C and V302C mutations (according to the EU numbering scheme) in its heavy chain.

[0180] In certain embodiments, the anti-TREM2 antibodies of the invention comprise a CH1 region and hinge region from a human IgG2 antibody and an Fc region from a human IgG1 antibody, wherein the Fc region comprises the amino acid sequence of:

APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKV
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF
YPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQ
GNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 281).

[0181] In other embodiments, the anti-TREM2 antibodies of the invention comprise a CH1 region and hinge region from a human IgG2 antibody and an Fc region from a human IgG1 antibody, wherein the Fc region comprises the amino acid sequence of:

APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKV
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF

YPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQ
GNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 282).

[0182] Modifications of the TREM2 agonist antigen binding proteins of the invention to increase serum half-life also may be desirable, for example, by incorporation of or addition of a salvage receptor binding epitope (e.g., by mutation of the appropriate region or by incorporating the epitope into a peptide tag that is then fused to the antigen binding protein at either end or in the middle, e.g., by DNA or peptide synthesis; *see, e.g.*, WO96/32478) or adding molecules such as PEG or other water soluble polymers, including polysaccharide polymers. The salvage receptor binding epitope preferably constitutes a region wherein any one or more amino acid residues from one or two loops of an Fc region are transferred to an analogous position in the antigen binding protein. Even more preferably, three or more residues from one or two loops of the Fc region are transferred. Still more preferred, the epitope is taken from the CH2 domain of the Fc region (e.g., an IgG Fc region) and transferred to the CH1, CH3, or VH region, or more than one such region, of the antigen binding protein. Alternatively, the epitope is taken from the CH2 domain of the Fc region and transferred to the CL region or VL region, or both, of the antigen binding protein. *See* International applications WO 97/34631 and WO 96/32478 for a description of Fc variants and their interaction with the salvage receptor.

[0183] In some embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain comprising the sequence of SEQ ID NO: 334 and a heavy chain comprising the sequence of SEQ ID NO: 335. In some embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain comprising the sequence of SEQ ID NO: 334 and a heavy chain comprising the sequence of SEQ ID NO: 336. In some embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain comprising the sequence of SEQ ID NO: 337 and a heavy chain comprising the sequence of SEQ ID NO: 338. In some embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain comprising the sequence of SEQ ID NO: 339 and a heavy chain comprising the sequence of SEQ ID NO: 340. In some embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain comprising the sequence of SEQ ID NO: 341 and a heavy chain comprising the sequence of SEQ ID NO: 342.

[0184] In some embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a light chain consisting of or consisting essentially of the amino acid sequence of

SEQ ID NO: 334, 337, 339 or 341. In some embodiments, the TREM2 agonist antigen binding proteins of the invention comprise a heavy chain consisting of or consisting essentially of the amino acid sequence of SEQ ID NO: 335, 336, 338, 340, or 342. In a specific embodiment, the TREM2 agonist antigen binding proteins of the invention comprise a light chain and a heavy chain, wherein (a) the light chain consisting of or consisting essentially of the amino acid sequence of SEQ ID NO: 334 and the heavy chain consisting of or consisting essentially of the amino acid sequence of SEQ ID NO: 335; (b) the light chain consisting of or consisting essentially of the amino acid sequence of SEQ ID NO: 334 and the heavy chain consisting of or consisting essentially of the amino acid sequence of SEQ ID NO: 336; (c) the light chain consisting of or consisting essentially of the amino acid sequence of SEQ ID NO: 337 and the heavy chain consisting of or consisting essentially of the amino acid sequence of SEQ ID NO: 338; (d) the light chain consisting of or consisting essentially of the amino acid sequence of SEQ ID NO: 339 and the heavy chain consisting of or consisting essentially of the amino acid sequence of SEQ ID NO: 340; or (e) the light chain consisting of or consisting essentially of the amino acid sequence of SEQ ID NO: 341 and the heavy chain consisting of or consisting essentially of the amino acid sequence of SEQ ID NO: 342.

[0185] In some embodiments, the TREM2 agonist antigen binding proteins of the invention are “bispecific” meaning that they are capable of specifically binding to two different antigens, human TREM2 and a second antigen. In certain embodiments, the second antigen is a protein that facilitates transport across the blood-brain barrier, such as a receptor that mediates blood-brain barrier transport. Such receptors include, but are not limited to, the insulin receptor, the transferrin receptor, the leptin receptor, the insulin-like growth factor (IGF) receptor, low density lipoprotein receptors (e.g. low density lipoprotein receptor-related protein 8 (LRP8), low density lipoprotein receptor-related protein 1 (LRP1), low density lipoprotein receptor-related protein 2 (LRP2)), heparin-binding epidermal growth factor-like growth factor, CD98 heavy chain (CD98hc), basigin, the human transmembrane protein 30A (TMEM30A), and Glucose Transporter Type 1 (Glut1). In one embodiment, the second antigen is the human insulin receptor. In one embodiment, the second antigen is the human insulin-like growth receptor. In another embodiment, the second antigen is the human transferrin receptor. In one embodiment, the second antigen is TMEM30A. In any of these instances, the human TREM2 binding domain could be at the N-terminal end or the C-terminal end of the multivalent bispecific (IgG-Fab, IgG-scFv), or expressed in the multi-

specific binding formats described in Spiess, C. et al., *Molecular Immunology* 67, 95-106 (2015) and Brinkman, U. et al., *MABS* 9(2)182-212 (2017).

[0186] In certain embodiments, the TREM2 agonist antigen binding proteins are multivalent. The valency of the binding protein denotes the number of individual antigen binding domains within the binding protein. For example, the terms “monovalent,” “bivalent,” and “tetravalent” with reference to the antigen binding proteins of the invention refer to binding proteins with one, two, and four antigen binding domains, respectively. Thus, a multivalent antigen binding protein comprises two or more antigen binding domains. In some embodiments, the bispecific antigen binding proteins of the invention are bivalent. Thus, such bispecific, bivalent antigen binding proteins contain two antigen binding domains: one antigen-binding domain binding to human TREM2 and one antigen-binding domain binding to a second antigen, such as an antigen that facilitates transport across the blood-brain barrier. In other embodiments, the bispecific antigen binding proteins are multivalent. For instance, in certain embodiments, the bispecific antigen binding proteins are trivalent or tetravalent comprising three or four antigen-binding domains: one or two antigen-binding domains binding to human TREM2 and one or two antigen-binding domains binding to a second antigen, such as an antigen that facilitates transport across the blood-brain barrier.

[0187] The term “antigen binding domain,” which is used interchangeably with “binding domain,” refers to the region of the antigen binding protein that contains the amino acid residues that interact with the antigen and confer on the antigen binding protein its specificity and affinity for the antigen. The binding domain may be derived from an antibody or functional fragment thereof that specifically binds to the antigen. In certain embodiments, the bispecific antigen binding proteins of the invention comprise one antigen-binding domain binding to human TREM2 and one antigen-binding domain binding to the human insulin receptor. In other embodiments, the bispecific antigen binding proteins of the invention comprise one antigen-binding domain binding to human TREM2 and one antigen-binding domain binding to the human transferrin receptor. In some embodiments, the bispecific antigen binding proteins of the invention comprise two antigen-binding domains binding to human TREM2 and two antigen-binding domains binding to the human insulin receptor. In other embodiments, the bispecific antigen binding proteins of the invention comprise two antigen-binding domains binding to human TREM2 and two antigen-binding domains binding to the human transferrin receptor. In one embodiment, the bispecific antigen binding proteins of the invention comprise one or two antigen-binding domains binding to human

TREM2 and one or two antigen-binding domains binding to the human insulin-like growth receptor. In one embodiment, the bispecific antigen binding proteins of the invention comprise one or two antigen-binding domains binding to human TREM2 and one or two antigen-binding domains binding to TMEM30A. The antigen binding domains binding to human TREM2 of the bispecific TREM2 agonist antigen binding proteins can be derived from any of the anti-TREM2 agonist antibodies described herein. The antigen binding domains binding to the human insulin receptor, the human insulin like growth receptor, TMEM30A, or the human transferrin receptor can be derived from monoclonal antibodies to these receptors known in the art, such as those described in US Patent No. 7,388,079; US Patent No. 8,663,598; and US Patent Publication No. 2015/0110791, Abulrob, A. *et al.*, *J. Neurochem.* 95, 1201–1214 (2005), and Muruganandam, A. *et al.*, *FASEB J.* 16, 240–242 (2002). In certain embodiments, the antigen binding domains binding to the human insulin receptor, the human insulin like growth receptor, TMEM30A, or the human transferrin receptor is a single domain antibody. In certain embodiments, the human TREM2 binding domain is at the N-terminal end or the C-terminal end of the multivalent bispecific (IgG-Fab, IgG-scFv), or expressed in the multi-specific binding formats known in the art, such as those described in Spiess, C. *et al.*, *Molecular Immunology* 67, 95-106 (2015) and Brinkman, U. *et al.*, *MABS* 9(2)182-212 (2017).

[0188] Methods of making bispecific antibodies are known in the art. One such method of making a “bispecific” antigen binding protein or antibody involves the fusion of hybridomas or linking of Fab’ fragments. *See, e.g.*, Songsivilai and Lachmann, 1990, *Clin. Exp. Immunol.* 79:315-321; Kostelny *et al.*, 1992, *J. Immunol.* 148:1547-1553. Another method involves engineering the Fc portion of the heavy chains such as to create “knobs” and “holes” which facilitate heterodimer formation of the heavy chains when co-expressed in a cell. *See, e.g.*, WO 96/027011. Still another method also involves engineering the Fc portion of the heavy chain but uses electrostatic steering to encourage heterodimer formation while discouraging homodimer formation of the heavy chains when co-expressed in a cell. *See, e.g.*, WO2009089004 and WO2014081955.

[0189] The present invention includes one or more isolated polynucleotides or isolated nucleic acids encoding the TREM2 agonist antigen binding proteins, such as the anti-TREM2 agonist monoclonal antibodies, described herein. In addition, the present invention encompasses vectors comprising the nucleic acids, host cells or cell lines comprising the nucleic acids, and methods of making the antigen binding proteins of the invention. The

nucleic acids comprise, for example, polynucleotides that encode all or part of an antigen binding protein, for example, one or both chains of an antibody of the invention, or a fragment, derivative, mutein, or variant thereof, polynucleotides sufficient for use as hybridization probes, PCR primers or sequencing primers for identifying, analyzing, mutating or amplifying a polynucleotide encoding a polypeptide, anti-sense oligonucleotides for inhibiting expression of a polynucleotide, and complementary sequences of the foregoing. The nucleic acids can be any length as appropriate for the desired use or function, and can comprise one or more additional sequences, for example, regulatory sequences, and/or be part of a larger nucleic acid, for example, a vector. Nucleic acid molecules of the invention include DNA and RNA in both single-stranded and double-stranded form, as well as the corresponding complementary sequences. DNA includes, for example, cDNA, genomic DNA, chemically synthesized DNA, DNA amplified by PCR, and combinations thereof. The nucleic acid molecules of the invention include full-length genes or cDNA molecules as well as a combination of fragments thereof. The nucleic acids of the invention can be derived from human sources as well as non-human species.

[0190] Relevant amino acid sequences from an immunoglobulin or region thereof (e.g. variable region, Fc region, etc.) or polypeptide of interest may be determined by direct protein sequencing, and suitable encoding nucleotide sequences can be designed according to a universal codon table. Alternatively, genomic or cDNA encoding monoclonal antibodies or binding fragments thereof of the invention can be isolated and sequenced from cells producing such antibodies (e.g. hybridomas) using conventional procedures, such as the methods described in Example 3.

[0191] An “isolated nucleic acid,” which is used interchangeably herein with “isolated polynucleotide,” is a nucleic acid that has been separated from adjacent genetic sequences present in the genome of the organism from which the nucleic acid was isolated, in the case of nucleic acids isolated from naturally-occurring sources. In the case of nucleic acids synthesized enzymatically from a template or chemically, such as PCR products, cDNA molecules, or oligonucleotides for example, it is understood that the nucleic acids resulting from such processes are isolated nucleic acids. An isolated nucleic acid molecule refers to a nucleic acid molecule in the form of a separate fragment or as a component of a larger nucleic acid construct. In one preferred embodiment, the nucleic acids are substantially free from contaminating endogenous material. The nucleic acid molecule has preferably been derived from DNA or RNA isolated at least once in substantially pure form and in a quantity

or concentration enabling identification, manipulation, and recovery of its component nucleotide sequences by standard biochemical methods (such as those outlined in Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1989)). Such sequences are preferably provided and/or constructed in the form of an open reading frame uninterrupted by internal non-translated sequences, or introns, that are typically present in eukaryotic genes. Sequences of non-translated DNA can be present 5' or 3' from an open reading frame, where the same do not interfere with manipulation or expression of the coding region. Unless specified otherwise, the left-hand end of any single-stranded polynucleotide sequence discussed herein is the 5' end; the left-hand direction of double-stranded polynucleotide sequences is referred to as the 5' direction. The direction of 5' to 3' production of nascent RNA transcripts is referred to as the transcription direction; sequence regions on the DNA strand having the same sequence as the RNA transcript that are 5' to the 5' end of the RNA transcript are referred to as "upstream sequences"; sequence regions on the DNA strand having the same sequence as the RNA transcript that are 3' to the 3' end of the RNA transcript are referred to as "downstream sequences."

[0192] The present invention also includes nucleic acids that hybridize under moderately stringent conditions, and more preferably highly stringent conditions, to nucleic acids encoding polypeptides as described herein. The basic parameters affecting the choice of hybridization conditions and guidance for devising suitable conditions are set forth by Sambrook, Fritsch, and Maniatis (1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., chapters 9 and 11; and *Current Protocols in Molecular Biology*, 1995, Ausubel *et al.*, eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4), and can be readily determined by those having ordinary skill in the art based on, for example, the length and/or base composition of the DNA. One way of achieving moderately stringent conditions involves the use of a prewashing solution containing 5 x SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0), hybridization buffer of about 50% formamide, 6 x SSC, and a hybridization temperature of about 55°C (or other similar hybridization solutions, such as one containing about 50% formamide, with a hybridization temperature of about 42°C), and washing conditions of about 60°C, in 0.5 x SSC, 0.1% SDS. Generally, highly stringent conditions are defined as hybridization conditions as above, but with washing at approximately 68°C, 0.2 x SSC, 0.1% SDS. SSPE (1 x SSPE is 0.15M NaCl, 10 mM NaH₂PO₄, and 1.25 mM EDTA, pH 7.4) can be substituted for SSC (1 x SSC is 0.15M NaCl

and 15 mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete. It should be understood that the wash temperature and wash salt concentration can be adjusted as necessary to achieve a desired degree of stringency by applying the basic principles that govern hybridization reactions and duplex stability, as known to those skilled in the art and described further below (*see, e.g., Sambrook et al., 1989*).

[0193] When hybridizing a nucleic acid to a target nucleic acid of unknown sequence, the hybrid length is assumed to be that of the hybridizing nucleic acid. When nucleic acids of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the nucleic acids and identifying the region or regions of optimal sequence complementarity. The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5 to 10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, $T_m (^{\circ}\text{C}) = 2(\# \text{ of A} + \text{T bases}) + 4(\# \text{ of G} + \text{C bases})$. For hybrids above 18 base pairs in length, $T_m (^{\circ}\text{C}) = 81.5 + 16.6(\log_{10} [\text{Na}^+]) + 0.41(\% \text{ G} + \text{C}) - (600/\text{N})$, where N is the number of bases in the hybrid, and $[\text{Na}^+]$ is the concentration of sodium ions in the hybridization buffer ($[\text{Na}^+]$ for 1 x SSC = 0.165M). Preferably, each such hybridizing nucleic acid has a length that is at least 15 nucleotides (or more preferably at least 18 nucleotides, or at least 20 nucleotides, or at least 25 nucleotides, or at least 30 nucleotides, or at least 40 nucleotides, or most preferably at least 50 nucleotides), or at least 25% (more preferably at least 50%, or at least 60%, or at least 70%, and most preferably at least 80%) of the length of the nucleic acid of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably at least 70%, at least 75%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, 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%, and most preferably at least 99.5%) with the nucleic acid of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing nucleic acids when aligned so as to maximize overlap and identity while minimizing sequence gaps as described in more detail above.

[0194] Variants of the antigen binding proteins, including the variants described herein, can be prepared by site-specific mutagenesis of nucleotides in the DNA encoding the polypeptide, using cassette or PCR mutagenesis or other techniques well known in the art, to

produce DNA encoding the variant, and thereafter expressing the recombinant DNA in cell culture as outlined herein. However, antigen binding proteins comprising variant CDRs having up to about 100-150 residues may be prepared by *in vitro* synthesis using established techniques. The variants typically exhibit the same qualitative biological activity as the naturally occurring analogue, e.g., binding to antigen. Such variants include, for example, deletions and/or insertions and/or substitutions of residues within the amino acid sequences of the antigen binding proteins. Any combination of deletion, insertion, and substitution is made to arrive at the final construct, provided that the final construct possesses the desired characteristics. The amino acid changes also may alter post-translational processes of the antigen binding protein, such as changing the number or position of glycosylation sites. In certain embodiments, antigen binding protein variants are prepared with the intent to modify those amino acid residues which are directly involved in epitope binding. In other embodiments, modification of residues which are not directly involved in epitope binding or residues not involved in epitope binding in any way, is desirable, for purposes discussed herein. Mutagenesis within any of the CDR regions, framework regions, and/or constant regions is contemplated. Covariance analysis techniques can be employed by the skilled artisan to design useful modifications in the amino acid sequence of the antigen binding protein. *See, e.g.*, Choulier, *et al.*, Proteins 41:475-484, 2000; Demarest *et al.*, J. Mol. Biol. 335:41-48, 2004; Hugo *et al.*, Protein Engineering 16(5):381-86, 2003; Aurora *et al.*, US Patent Publication No. 2008/0318207 A1; Glaser *et al.*, US Patent Publication No. 2009/0048122 A1; Urech *et al.*, WO 2008/110348 A1; Borrás *et al.*, WO 2009/000099 A2. Such modifications determined by covariance analysis can improve potency, pharmacokinetic, pharmacodynamic, and/or manufacturability characteristics of an antigen binding protein.

[0195] Table 6 shows exemplary nucleic acid sequences encoding the light and heavy chain variable regions of anti-TREM2 antibodies described herein. Polynucleotides encoding the anti-TREM2 antibody variable regions can be used to construct the antigen binding proteins described herein.

Table 6. Exemplary Anti-TREM2 Antibody Variable Region Nucleic Acid Sequences

Ab ID.	VL or VH Group Designation	Nucleic Acid Sequence	SEQ ID NO:
<i>Light chain variable regions</i>			

Ab ID.	VL or VH Group Designation	Nucleic Acid Sequence	SEQ ID NO:
12G10	LV-01	CAGGCTGTGCCGACTCAGCCGCTCTCCCTCTCTGCATCTCCTGGAGTATT AGCCAGTCTCACCTGCACCTTACGCAGTGGCATCAATGTTGGTACCTAC AGGATATACTGGTACCAGCAGAAGCCAGGGAGTCTCCCCAGTATCTCC TGAGGTACAAATCAGACTCAGATAAGCAGCAGGGCTCTGGAGTCCCCA GCCGCTTCTCTGGATCCAAGGATGCTTCGGCCAATGCAGGGATTCTTACT CATCTCTGGGCTCCAGTCTGAGGATGAGGCTGACTATTACTGTATGATT TGGTACAGCAGTGTGTGGTATTTCGGCGGAGGGACCAAACTGACCGTC CTA	208
26A10	LV-02	TCCTATGAGCTGACTCAGCCACCCTCAGTGTCCGTGTCCCCAGGACAGA CAGCCAGCATCACCTGCTCTGGAGATAAAATTGGGAGATAAGTATGTTTG CTGGTATCAGCAGAAGCCAGGCCAGTCCCCTGTGCTGGTCATCTATCAA GATAGCAAGCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCAACT CTGGGAACACAGCCACTCTGACCATCAGCGGGACCCAGGCTATGGATG AGGCTGACTATTACTGTCTAGGCGTGGGACAGTAACACTGTGGTATTTCGG CGGAGGGACCAAGCTGACCGTCCTA	209
26C10	LV-03	TCCTTTGAGCTGACTCAGCCACCCTCAGTGTCCGTGTCCCCAGGACAGA CAGCCAGCATCACCTGCTCTGGAGATAAAATTGGGGGATAAGTATGTTTG CTGGTATCAGCAGAAGCCAGGCCAGTCCCCTATGTTGGTCATCTATCAA GATACCAAGCGGCCCTCAGGGATCCCTGAACGATTCTCTGGCTCCAACT CTGGGAACACAGCCACTCTGACCATCAGCGGGACCCAGGCTATGGATG AGGCTGACTATTACTGTCTAGGCGTGGGACAGCAGCACTGTGGTCTTCGG CGGAGGGACCAAGCTGACCGTCCTA	210
26F2	LV-04	TCCTATGAGCTGACTCAGCCACCCTCAGTGTCCGTGTCCCCAGGACAGA CAGCCAGCATCACCTGCTCTGGAGATAAAATTGGGGGATAAGTATGTTTG CTGGTATCAGCAGAAGCCAGGCCAGTCCCCTGTGTTGGTCATCTTTCAA GATAGCAAGCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCAACT CTGGGAACACAGCCACTCTGACCATCAGCGGGACCCAGGCTATGGATG AGGCTGACTATTACTGTCTAGGCGTGGGACAGCAGCACTGTGGTATTTCGG CGGAGGGACCAAGCTGACCGTCCTA	211
33B12	LV-05	TCCTATGAGCTGACTCAGCCACCCTCAGTGTCCGTGTCCCCAGGACAGA CAGCCAGCATCACCTGCTCTGGAGATAAAATTGGGGGATAAGTATGTTTG CTGGTATCAGCAGAAGCCAGGCCAGTCCCCTGTGTTGGTCATCTATCAA GATAGCAAGCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCAACT CTGGGAACACAGCCACTCTGACCATCAGCGGGACCCAGGCTATGGATG AGGCTGACTATTACTGTCTAGGCGTGGGACAGTAGCACTGTGGTATTTCGG CGGAGGGACCAAGCTGACCGTCCTA	212
24C12	LV-06	GGCATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCG AGAGGGCCACCATCAACTGCAAGTCCAGCCGAGTGTTTTGTACAGCTC CAACAATAAGAACTACTTAGCTTGGTACCAGCAGAAACCAGGACAGCC TCCTAAGGTGCTCATTACTGGGCATCTACCCGGGAATCCGGGGTCCCT GACCGATTCACTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCA GCAGCCTGCAGGCTGAAGATGTGGCAGTTTATAACTGTCAGCAATATTA TATTACTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAATA	213
24G6	LV-07	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCG AGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATACAGCTC CAACAATAAGCACTTCTTAGCTTGGTACCAGCAGAAACCAGGACAGCC TCCTAAGCTGCTCATTACTGGGCATCTACCCGGGAGTCCGGGGTCCCT GACCGATTCACTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCA GCAGCCTGCAGGCTGAAGATGTGGCAGTTTATAACTGTCAGCAATATTA TAGTACTCCGCTCACTTTCGGCGGAGGGACCAAGTGGAGATCAAA	214
24A10	LV-08	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCG AGAGGGCCACCATCACCTGCAAGTCCAGCCACAATGTTTTATACAGCTC CAACAATAAGAACTACTTAGCTTGGTATCAGCAGAAACCAGGACAGCC TCCTAAACTGCTCATTACTGGGCATCTACCCGGGAATCCGGGGTCCCT GACCGATTCACTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCA	215

Ab ID.	VL or VH Group Designation	Nucleic Acid Sequence	SEQ ID NO:
		GCAGCCTGCAGGCTGAAGATGTGGCAGTTTATTACTGTACCAATATTATAGTACTCCGTGCAGTTTTGGCCAGGGGACCAAGCTGGAGATCAAA	
10E3	LV-09	GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAACTTAGCCTGGTTCCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGCTTCCACCAGGGCCACTGGTATTCCAGCCAGGTTTCAGTGTCAAGTGGTCTGGGACAGAGTTCACTCTCACCATCAGCAGCCTGCAGTCTGAAGATTTTGCATTTTATTACTGTCTGCAGGATAATAATTGGCCTCCCACTTTGCGCCCTGGGACCAAGTGGATATCAAA	216
13E7	LV-10	GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAACTTAGCCTGGTTCCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGCTTCCACCAGGGCCACTGGTATTCCAGCCAGGTTTCAGTGTCAAGTGGTCTGGGACAGAGTTCACTCTCACCATCAGCAGCCTGCAGTCTGAAGATTTTGCAGTTTATTACTGTCTGCAGGATAATAATTGGCCTCCCACTTTGCGCCCTGGGACCAAGTGGATATCAAA	217
25F12	LV-11	GAAAAAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAACAACAACCTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGCATCCACCAGGGCCACTGGTATCCAGCCAGGTTTCAGTGGCAGTGGTCTGGGACAGAGTTCACTCTCACCATCAGCAGCCTGCAGTCTGAAGATTTTGCAGTTTATTACTGTCTCAGCAGTATAATAACTGGCCTCGGACGTTGCGCCAAGGGACCAAGGTGGAAATCAAA	218
32E3	LV-12	GAATTTGTGTTGACGCAGTCTCCAGCCACCCTGTCTTTGTCTCCGGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGATTATTAGCAGCAACTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATAGTGCATCCAGCAGGGCCACTGGCATCCAGACAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTTCCTCTCACCATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCTCAGCAGTTTGATAGCTCACCGATCACCTTCGGCCGAGGGACACGACTGGACATTAAA	219
24F4	LV-13	GAAATTGTGTTGACGCAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCAGACAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTTCCTCTCACCATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCTCAGCAGTATGATACCTCACCATTCCTTTCGGCCCTGGGACCAAGTGGATATCAAA	220
16B8	LV-14	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGTCTGGGCGAGTCAGGGTATTAGCAACTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCTCTTTGCAAACTGGGGTCCCTTCAAGGTTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTACTCTTGTCAACAGTCTAACAGTTTCCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA	221
4C5	LV-15	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGTCTGGGCGAGTCAGGGTATTAGCAACTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCAAGTTGGGGTCCATTAAAGGTTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTACTATTGTCAACAGGCTGACAGTTTCCCTCGCAATTTGGCCAGGGGACCAAGCTGGAGATCAAA	222
6E7 V9 V30 V33 V44	LV-16	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGTCTGGGCGAGTCAGGGTATTAGCAGCTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCAAAATGGGGTCCCATCAAGGTTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAG	223

Ab ID.	VL or VH Group Designation	Nucleic Acid Sequence	SEQ ID NO:
V68		ATTTTGCAACTTACTTTTGTCAACAGGCTGACAGTTTCCCTCGCACTTTT GGCCAGGGGACCAAGCTGGAGATCAAA	
5E3	LV-17	GACATCCAGATGACCCAGTCTCCATCCTCACTGTCTGCATCTGTAGGAG ACAGAGTCACCATCACTTGTCTGGGCGAGTCAGGGCATTAGCAATTATTT AGCCTGGTTTCAGCAGAAACCAGGGAAAGCCCCCTAAATCCCTGATCTAT GCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAAGTTCAGCGGCAGTG GATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGA TTTTGCAACTTATTACTGCCAACAGTATAGTACTTACCCATTCACTTTTCG GCCCTGGGACCAAGTGGATATCAAA	224
4G10	LV-18	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAG ACAGAGTCACCATCACTTGTCCGGGCAAGTCAGGGCATAAGAAATGATT TAGGCTGGTATCAGCAGAAACCAGGGAATGCCCTAAGCGCCTGATCT ATGCTGCATCCAGTTTGCCAAGTGGGGTCCCATCAAAGTTTCAGCGGCAG TGGATCTGGGCCAGAATTCCTCTCACAATCAGCAGTCTGCAGCCTGAA GATTTTGCAACTTATTACTGTCTACAGCATAATAGTTACCCGTGGACGTT CGGCCAAGGGACCAAGGTGGAAATCACA	225
V3	LV-101	GACATCCAGATGACCCAGTCTCCATCTCCGTGTCTGCATCTGTAGGAG ACAGAGTCACCATCACTTGTCTGGGCGAGTCAGGGTATTAGCAGCTGGTT AGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCCTAAGCTCCTGATCTA TGCTGCATCCAGTAGGCAAAATGGGGTCCCATCAAAGTTTCAGCGGCAG TGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAA GATTTTGCAACTTACTTTTGTCAACAGGCTGACAGGTTCCCTCGCACTTT TGGCCAGGGGACCAAGCTGGAGATCAAA	226
V24	LV-102	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAG ACAGAGTCACCATCACTTGTCTGGGCGAGTCAGGGTATTAGCAGCTGGTT AGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCCTAAGCTCCTGATCTA TGCTGCATCCAGTTTGCAAAGGGGGTCCCATCAAAGTTTCAGCGGCAGT GGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAG ATTTTGCAACTTACTTTTGTCAACAGGCTGACAGTTTCCCTCATACTTTT GGCCAGGGGACCAAGCTGGAGATCAAA	227
V27	LV-103	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAG ACAGAGTCACCATCACTTGTCTGGGCGAGTCAGGGTATTAGCAGCTGGTT AGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCCTAAGCTCCTGATCTA TGCTGCATCCAGTTTGCAACGTGGGGTCCCATCAAAGTTTCAGCGGCAGT GGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAG ATTTTGCAACTTACTTTTGTCAACAGGCTGACAGTTTCCCTCGCACTTTT GGCCAGGGGACCAAGCTGGAGATCAAA	228
V40	LV-104	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAG ACAGAGTCACCATCACTTGTCTGGGCGAGTCAGGGTATTAGCAGCTGGTT AGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCCTAAGCTCCTGATCTA TGCTGCATCCAGTTTGCAACTTGGGGTCCCATCAAAGTTTCAGCGGCAGT GGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAG ATTTTGCAACTTACTTTTGTCAACAGGCTGACCGTTTCCCTCGCACTTTT GGCCAGGGGACCAAGCTGGAGATCAAA	229
V48	LV-105	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAG ACAGAGTCACCATCACTTGTCTGGGCGAGTCAGGGTATTAGCAGCTGGTT AGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCCTAAGCTCCTGATCTA TGCTGCATCCAGTTTGCAAACGGGGTCCCATCAAAGTTTCAGCGGCAGT GGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAG ATTTTGCAACTTACTTTTGTCAACAGGCTGACAGTTTGCCTCGCACTTTT GGCCAGGGGACCAAGCTGGAGATCAAA	230
V49	LV-106	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAG ACAGAGTCACCATCACTTGTCTGGGCGAGTCAGGGTATTAGCAGCTGGTT AGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCCTAAGCTCCTGATCTA TGCTGCATCCAGTCTGGCAAATGGGGTCCCATCAAAGTTTCAGCGGCAGT GGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAG	231

Ab ID.	VL or VH Group Designation	Nucleic Acid Sequence	SEQ ID NO:
		ATTTTGCAACTTACTTTTGTCAACAGGCTGACAGTTATCCTCGCACTTTT GGCCAGGGGACCAAGCTGGAGATCAAA	
V52	LV-107	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAG ACAGAGTCACCATCACTTGTGCGGCGAGTCAGGGTATTAGCAGCTGGTT AGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTA TGCTGCATCCAGTTTGCAAAGGGGGTCCCATCAAGGTTTCAGCGGCAGT GGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAG ATTTTGCAACTTACTTTTGTCAACAGGCTGACCGTTTCCCTCGCACTTTT GGCCAGGGGACCAAGCTGGAGATCAAA	232
V60	LV-108	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAG ACAGAGTCACCATCACTTGTGCGGCGAGTCAGGGTATTAGCAGCTGGTT AGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTA TGCTGCATCCAGTTTGCAAAGGGGGTCCCATCAAGGTTTCAGCGGCAGT GGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAG ATTTTGCAACTTACTTTTGTGGGCGAGGCTGACAGTTTCCCTCGCACTTTT GGCCAGGGGACCAAGCTGGAGATCAAA	233
V73	LV-106	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAG ACAGAGTCACCATCACTTGTGCGGCGAGTCAGGGTATTAGCAGCTGGTT AGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTA TGCTGCATCCAGTCGTCAAATGGGGTCCCATCAAGGTTTCAGCGGCAGT GGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAG ATTTTGCAACTTACTTTTGTCAACAGGCTGACAGTTATCCTCGCACTTTT GGCCAGGGGACCAAGCTGGAGATCAAA	234
V76	LV-109	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAG ACAGAGTCACCATCACTTGTGCGGCGAGTCAGGGTATTAGCAGCTGGTT AGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTA TGCTGCATCCAGTTTGCAAAGGGGGTCCCATCAAGGTTTCAGCGGCAGT GGATCTGGGAGAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAG ATTTTGCAACTTACTTTTGTCAACAGGCTGACAGTTTCCCTCGCACTTTT GGCCAGGGGACCAAGCTGGAGATCAAA	235
V84	LV-110	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAG ACAGAGTCACCATCACTTGTGCGGCGAGTCAGGGTATTAGCAGCTGGTT AGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTA TGGTGCATCCAGTTTGCAAATGGGGTCCCATCAAGGTTTCAGCGGCAGT GGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAG ATTTTGCAACTTACTTTTGTCAACAGGCTGACAGTTTCCCGCGCACTTTT GGCCAGGGGACCAAGCTGGAGATCAAA	236
V10	LV-201	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAG ACAGAGTCACCATCACTTGTGCGGCGAGTCAGGGTATTAGCAGCTGGTT AGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTA TTCTGCATCCAGTTTGCAAATGGGGTCCCATCAAGGTTTCAGCGGCAGT GGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAG ATTTTGCAACTTACTTTTGTCAACAGGCTGACAGTTTCCCTCGCACTTTT GGCCAGGGGACCAAGCTGGAGATCAAA	313
V23	LV-202	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAG ACAGAGTCACCATCACTTGTGCGGCGAGTCAGGGTATTAGCAGCTGGTT AGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTA TGCTGCATCCAGTTTGCAAATGGGGTCCCATCAAGGTTTCAGCGGCAGT GGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAG ATTTTGCAACTTACTTTTGTCAACAGGCTGACAGTTTCCCTCTTACTTTT GGCCAGGGGACCAAGCTGGAGATCAAA	314
V57	LV-203	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAG ACAGAGTCACCATCACTTGTGCGGCGAGTCAGGGTATTAGCAGCTGGTT AGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTA TGCTGCATCCAGTTTGCAAATGGGGTCCCATCAAGGTTTCAGCGGCAGT GGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAG	315

Ab ID.	VL or VH Group Designation	Nucleic Acid Sequence	SEQ ID NO:
		ATTTTGCAACTTACTTTTGTCAACAGGCTGACAGTTTCCCTCGCACTTTTGGCCAGGGGACCAAGCTGGAGATCAAA	
V70	LV-204	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGTCTGGGCGAGTCAGGGTATTAGCAGCTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCAGGGAGTTTGCAAAATGGGGTCCCATCAAGGTTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTACTTTTGTCAACAGGCTGACAGTTTCCCTCGCACTTTTGGCCAGGGGACCAAGCTGGAGATCAAA	316
V83	LV-205	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGTCTGGGCGAGTCAGGGTATTAGCAGCTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCAAAATGGGGTCCCATCAAGGTTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTACTTTTGTCAACAGGCTGTGAGTTTCCCTCGCACTTTTGGCCAGGGGACCAAGCTGGAGATCAAA	317
V90	LV-206	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGTCTGGGCGAGTCAGGGTATTAGCAGATGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCAAAATGGGGTCCCATCAAGGTTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTACTTTTGTCAACAGGCTGACAGTTTCCCTCGCACTTTTGGCCAGGGGACCAAGCTGGAGATCAAA	318
<i>Heavy chain variable regions</i>			
12G10 24C12	HV-01	GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAGCTATGCCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGCTATTGGTGGTGGTGGTGTAGCACATACTGCGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAATACGCTGTATCTGCAAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGA AATTTTATATAGCAGTGGCTGGTTCTCACTTTGACTACTGGGGCCAGGG AACCCTGGTCACCGTCTCCTCA	237
26A10	HV-02	GAGGTGCAACTGGTGGAGTCTGGGGGAGCCTTGGTACAGCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTAGATTACCTTCAGTAGCTTTGGCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTATACATTAGTAGTAGTAGTTTTACCATATATTACGCAGACTCTGTGAAGGGCCGATTACCATCTCCAGAGACAATGCCAAGAATTCATTCTATCTGCAAAATGAACAGCCTGAGAGACGAGGACACGGCTGTGTATTACTGTGCGA GAGAGGGGGGTCTTACTATGGTTTCGGGGAGTCTCTTCCTACGGTTTGGA CGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA	238
26C10	HV-03	GAGGTGCAACTGGTGGAGTCTGGGGGAGCCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTAGCTTTGGCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTATACATTAGTAGTAGTAGTTTTACCATATACTACGCAGACTCTGTGAAGGGCCGATTACCATCTCCAGAGACAATGCCAAGAATTCGTTCTATCTGCAAAATGAACAGCCTGAGAGACGAGGACACGGCTGTGTATTCTGTGTGA GAGAGGGGGGTATAACTATGGTTTCGGGGAGTCTCTTCCTACGGTATGGA CGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA	239
26F2	HV-04	GAGGTGCAACTGGTGGAGTCTGGGGGAGCCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTAGCTTTGGCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTATACATTAGTAGTAGTAGTTTTACCATATACTACGCAGACTCTGTGAAGGGCCGATTACCATCTCCAGAGACAATGCCAAGAATTCATTCTATCTGCAAAATGAACAGCCTGAGAGACGAGGACACGGCTGTGTATTCTGTGCGA GAGAGGGGGGTATTACTATGGTTTCGGGGAGTCTCTTCCTACGGTATGGA CGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA	240

Ab ID.	VL or VH Group Designation	Nucleic Acid Sequence	SEQ ID NO:
33B12	HV-05	GAGGTGCAACTGGTGGAGTCTGGGGGAGCCTTGGTACAGCCTGGGGGG TCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTAGCTTTGG CATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGCCTGGAGTGGGTTTC ATACATTAGTAAAAGTAGTTTTACCATATACTACGCAGACTCTGTGAAG GGCCGATTACCATCTCCAGAGACAATGCCAAGAATTCACTCTATCTGC AAATGAACAGCCTGAGAGACGAGGACACGGCTGTGTATTACTGTGCGA GAGAGGGGGGTCTTACTATGGTTCGGGGAGTCTCTTCTACGGTTTGA CGTCTGGGGCCAAGGGACCACGGTCACCGTCTCTCTCA	241
24G6	HV-06	GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGG TCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAGCTATGC CATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGGTCTC AGCTATTAGTGGTAGTGGTGGTAGCACATACTACGCAGACTCCGTGAAG GGCCGGTTACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGC AAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGA AGGCGTATACACCTATGGCATTCTTTGACTACTGGGGCCAGGGAACCT GGTCACCGTCTCTCTCA	242
24A10	HV-07	GAGGTGCAGGTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGG TCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAACTATGC CATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTC AGCTATTAGTGGTAGTGGTGGTAGCACATACTACGCAGACTCCGTGAAG GGCCGGTTACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGC AAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGA AAGGAGGGTGGGAGCTATTTTACTGGGGCCAGGGAACCTGGTCACCG TCTCTCTCA	243
10E3	HV-08	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGATGATCTCCTGTAAGGGTTCTGGATACAGCTTTACCAACTACTG GATCGGCTGGGTGCGCCAGATGCCCGGGAAGGCCTGGAGTGGATGGG GATCATCTATCCTGGAGACTCTGATACCAGATAACAGCCCGTCTTCCAA GGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACCGCCTACCTGC AGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGCGAG ACGGAGACAGGGGATCTGGGGTGTATGCTCTTGATATCTGGGGCCAAGG GACATTGGTCACCGTCTCTTCA	244
13E7	HV-09	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGATGATCTCCTGTAAGGGTTCTGGATACAGCTTTACAGCTACTG GATCGGCTGGGTGCGCCAGATGCCCGGGAAGGCCTGGAGTGGATGGG GATCATCTATCCTGGAGACTCTGATACCAGATAACAGCCCGTCTTCCAA GGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACCGCCTACCTGC AGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGCGAG ACGGAGACAGGGGATCTGGGGTGTATGCTCTTGATTTCTGGGGCCAAGG GACATTGGTCACCGTCTCTTCA	245
25F12	HV-10	CAGGTGCAGCTACAGCAGTGGGGCGCAGGACTGTTGAAGCCTTCGGAG ACCCTGTCCCTACCTGCGCTGTCTATGGTGGGTCTTCAGTAGTTACTA CTGGAGCTGGATCCGCCAGCCCCAGGGAAGGGGCTGGAGTGGATTGG GGAAATCAATCATAGTGAAACACCAACTACAACCCGTCCCTCAAGAG TCGAGTCAACATATCAGTAGACACGTCCAAGAACCAGTTCTCCCTGAAG CTGAGCTCTGTGACCGCCGCGGACACGGCTGTGTATTACTGTGCGAGAG AGGGGTATTACGATATCTTGACTGGTTATCATGATGCTTTTGATATTTGG GACCAAGGGACAATGGTCACCGTNTTTTCA	246
32E3	HV-11	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGCTTTACAGCTACT GGATCGGCTGGGTGCGCCAGATGCCCGGGAAGGCCTGGAGTGGATGG GGATCATCTATCCTGGTACTCTGATACCAGATAACAGCCCGTCTTCCA AGGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACCGCCTACCTG CAGTGGAGCACCTGAAGGCCTCGGACACCGCCATATATTACTGTGCGC GACATGACATTATACCAGCAGCCCTGGTGTCTTTGATATCTGGGGCCA AGGGACAATGGTCACCGTCTCTTCA	247

Ab ID.	VL or VH Group Designation	Nucleic Acid Sequence	SEQ ID NO:
24F4	HV-12	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACACCTTTACCAGCTACT GGATCGGCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGG GGATCATCTATCCTGGTGACTCTGATACCAGATACAGCCCGTCCTTCCA AGGCCAGGTCACCATCTCAGTCGACAAGTCCAGCAGCACCGCCTACCTG CAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATATATTACTGTACG AGACAGGCCATAGCAGTGACTGGTTTGGGGGGTTTCGACCCCTGGGGC CAGGGAACCCTGGTCAACCGTCTCCTCA	248
16B8	HV-13	CAGGTTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCC TCAGTGAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAACTATG GTATCAGCTGGGTGCGACAGGCCCCCTGGACAAGGGCTTGAGTGGATGG GATGGATCAGCGCTTACAATGGTAACACAACTATGCACAGAAGCTCC AGGGCAGAGTCACCATGACCACAGACACATCCACGAGTACAGTCTACA TGGAGCTGAGGAGCCTGAGATCTGACGACACGGCCGTGTATTACTGTGC GAGACGGGGATACAGCTATGGTTTCCTTTGACTACTGGGGCCAGGGAAC CCTGGTCAACCGTCTCCTCA	249
4C5	HV-14	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGAAGATCTCCTGTAAGGGTTCTGGACACAGTTTTACCAACTACT GGATCGCCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGG GGATCATCTATCCTGGTGACTCTGATACCAGATACAGCCCGTCCTTCCA AGGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACCGCCTACCTG CAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCGTGTATTTCTGTGCGA GACAAAGGACGTTTTACTATGATAGTAGTGTTATTTTGACTIONTGGGG CCAGGGAACCCTGGTCAACCGTCTCCTCA	250
6E7	HV-15	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGTTTTACCAGCTACT GGATCGCCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGG GGATCATCTATCCTGGTGACTCTGATACCAGATACAGCCCGTCCTTCCA AGGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACCGCCTACCTA CAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGCGA GACAAAGGACGTTTTATTATGATAGTAGTGATTATTTTGACTIONTGGGG CCAGGGAACCCTGGTCAACCGTCTCCTCA	251
5E3	HV-16	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCC TCAGTGAAGGTCTCCTGCAAGGCTTCTGGATACACCTTACCGGCTACT ATATACACTGGGTGCGACAGGCCCCCTGGACTAGGGCTTGAGTGGATGG GATGGATCAACCCTTACAGTGGTGCCACAACCTCTGCACAGAAGTTTCA GGGCAGGGTCACCATGACCAGGGACACGTCCATCAGCTCAGCCTACAT GGAAGTGAAGCAGGCTGAGATCTGACGACACGGCCGTGTATTACTGTGC GAGAGATGGAGGCTACCTGGCCCTCTACGGTACGGACGTCTGGGGCCA AGGGACCACGGTCAACCGTCTCCTCA	252
4G10	HV-17	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGCTTTCCAGCTACT GGATCGCCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGG GGATCATCTATCCTGGTGACTCTGATACCAGATACAGCCCGTCCTTCCA AGGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACCGCCTTTTTG AAGTGGAGTAGCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGCGC GACAGGGTATAGAAGTGACTGGTACGGGAGGTTTGGACGTCTGGGGCC AAGGGACCACGGTCAACCGTCTCCTCA	253
V3	HV-101	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGTTTTGCGAGCTACT GGATCGCCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGG GGATCATCTATCCTGGTGACTCTGATACCAGATACAGCCCGTCCTTCCA AGATCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACCGCCTACCTA CAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGCGA GAGGGAGGACGTTTTATTATGATAGTAGTGATTATTTTGACTIONTGGGG CCAGGGAACCCTGGTCAACCGTGTCTCA	254

Ab ID.	VL or VH Group Designation	Nucleic Acid Sequence	SEQ ID NO:
V24	HV-102	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGTTTTACCAGCTACT GGATTGCCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGG GGATCATCTATCCTGGTGACTCTGATGTGAGATACAGCCCGTCCTTCCA AGGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACC GCCTACCTA CAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGCGA GATCTAGGACGTTTTATTATGATAGTAGTGATTATTTTGACTACTGGGG CCAGGGAACCCCTGGTCAACCGTGTCTCA	255
V27	HV-103	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGTTTTACCAGCTACT GGATCGCCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGG GGATCATCTATCCTGGTGACTCTGATACCAGATACGCTCCGTCCTTCCA AGGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACC GCCTACCTA CAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGTGA GAAGTAGGACGTTTTATTATGATAGTAGTGATTATTTTGACTACTGGGG CCAGGGAACCCCTGGTCAACCGTGTCTCA	256
V40	HV-104	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGTTTTGGGAGCTACT GGATCGCCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGG GGATCATCTATCCTGGTGACTCTGATGTAGATACAGCCCGTCCTTCCA AGGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACC GCCTACCTA CAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGCGA GACAAAGGACGTTTTATTATGATAGTAGTGATTATTCGGACTACTGGGG CCAGGGAACCCCTGGTCAACCGTGTCTCA	257
V48	HV-105	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGTTTTGGTAGCTACT GGATCGCCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGG GGATCATCTATCCTGGTGACTCTGATGTGAGATACAGCCCGTCCTTCCA AGGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACC GCCTACCTA CAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGCGA GAATGAGGACGTTTTATTATGATAGTAGTGATTATTTTGACTACTGGGG CCAGGGAACCCCTGGTCAACCGTGTCTCA	258
V49	HV-106	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGTTTTAATAGCTACT GGATCGCCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGG GGACGATCTATCCTGGTGACTCTGATACCAGACTGAGCCCGTCCTTCCA AGGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACC GCCTACCTA CAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGCGA GAAGTAGGACGTTTTATTATGATAGTAGTGATTATTTTGACTACTGGGG CCAGGGAACCCCTGGTCAACCGTGTCTCA	259
V52	HV-107	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGTTTTGAGAGCTACT GGATCGCCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGG GGATCATCTATCCTGGTGACTCTGATACCAGATACAGCCCGTCCTTCCA AGGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACC GCCTACCTA CAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGCGA GAGGGAGGACGTTTTATTATGATAGTAGTGATTATTTTGACTACTGGGG CCAGGGAACCCCTGGTCAACCGTGTCTCA	260
V60	HV-108	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACCATTTTTACCAGCTACTG GATCGCCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGGG GATCATCTATCCTGGTGACTCTGATGTGAGATACAGCCCGTCCTTCCAA GGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACC GCCTACCTAC AGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGCGAG ACAAAGGACGTTTTATTATGATAGTAGTGATTATAGTGACTACTGGGGC CAGGGAACCCCTGGTCAACCGTGTCTCA	261

Ab ID.	VL or VH Group Designation	Nucleic Acid Sequence	SEQ ID NO:
V73	HV-109	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGTTTTGGTAGCTACT GGATCGCCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGG GGATCATCTATCCTGGTGACTCTGATACCAGATACAGCCCGGGGTTCCA AGGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACC GCCTACCTA CAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGCGA GAGGGAGGACGTTTTATTATGATAGTAGTGATTATTTTGA CTACTGGGG CCAGGGAACCCTGGTCAACCGTGTCCTCA	262
V76	HV-110	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGTTTTGGGAGCTACT GGATCGCCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGG GGATCATCTATCCTGGTGACTCTGATACCAGATACAGCCCGGAGTTCCA AGGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACC GCCTACCTA CAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGCGA GACAAAGGACGTTTTATTATGATAGTAGTGATTATAGTGACTACTGGGG CCAGGGAACCCTGGTCAACCGTGTCCTCA	263
V84	HV-111	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACGGGTTTACCAGCTACT GGATCGCCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGG GGATCATCTATCCTGGTGACAGTGATACCAGATACAGCCCGTCCTTCCA AGGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACC GCCTACCTA CAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGCGA GACAAAGGACGTTTTATTATGATAGTAGTGATTATTCGGACTACTGGGG CCAGGGAACCCTGGTCAACCGTGTCCTCA	264
V9	HV-201	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGTTTTACCAGCTACT GGATCGCCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGG GGATCATCTATCCTGGTGACTCTGATACCAGATACAGCCCGTCCTTCCA AGGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACC GCCTACCTA CAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGCGA GACAAAGGGGGTTTTATTATGATAGTAGTGATTATTTTGA CTACTGGGG CCAGGGAACCCTGGTCAACCGTGTCCTCA	319
V10 V23 V57 V70 V83	HV-15	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGTTTTACCAGCTACT GGATCGCCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGG GGATCATCTATCCTGGTGACTCTGATACCAGATACAGCCCGTCCTTCCA AGGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACC GCCTACCTA CAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGCGA GACAAAGGACGTTTTATTATGATAGTAGTGATTATTTTGA CTACTGGGG CCAGGGAACCCTGGTCAACCGTGTCCTCA	320
V30	HV-202	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGAAGATCTCCTGTAAGGGTTCTGGATCGAGTTTTACCAGCTACT GGATCGCCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGG GGATCATCTATCCTGGTGACTCTGATACCAGATACAGCCCGTCCTTCCA AGGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACC GCCTACCTA CAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGCGA GACAAAGGACGTTTTATTATGATAGTAGTGATTATTTTGA CTACTGGGG CCAGGGAACCCTGGTCAACCGTGTCCTCA	321
V33	HV-203	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGTTTTACCAGCTACT GGATCGCCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGG GGATCATCTATCCTGGTGACTCTGATACCAGATACAGCCCGTCCTTCCA AGGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACC GCCTACCTA CAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGCGA GACAAAGGACGTTTTATGGGGATAGTAGTGATTATTTTGA CTACTGGGG CCAGGGAACCCTGGTCAACCGTGTCCTCA	322

Ab ID.	VL or VH Group Designation	Nucleic Acid Sequence	SEQ ID NO:
V44	HV-204	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGTTTTACCAGCTACT GGATCGCCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGG GGATCATCTATCCTAGTGACTCTGATACCAGATACAGCCCGTCCTTCCA AGGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACCGCCTACCTA CAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGCGA GACAAAGGACGTTTTATTATGATAGTAGTGATTATTTTGACTIONTGGGG CCAGGGAACCCTGGTCAACCGTGTCTCA	323
V68	HV-205	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGTTTTACCAGCTACT GGATCGCCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGG GGATCATCTATCCTGGTGACTCTGATACCAGATACAGCCCGTCCTTCCA AGGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACCGCCTACCTA CAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGCGA GACAAAGGACGTTTAGGTATGATAGTAGTGATTATTTTGACTIONTGGGG CCAGGGAACCCTGGTCAACCGTGTCTCA	324
V90	HV-206	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAG TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGTTTTACCAGCGAGT GGATCGCCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGG GGATCATCTATCCTGGTGACTCTGATACCAGATACAGCCCGTCCTTCCA AGGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACCGCCTACCTA CAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGCGA GACAAAGGACGTTTTATTATGATAGTAGTGATTATTTTGACTIONTGGGG CCAGGGAACCCTGGTCAACCGTGTCTCA	325

[0196] Isolated nucleic acids encoding the anti-TREM2 binding domain of the antigen binding proteins of the invention may comprise a nucleotide sequence that is at least 80% identical, at least 90% identical, at least 95% identical, or at least 98% identical to any of the nucleotide sequences listed in Table 6. In some embodiments, an isolated nucleic acid encoding an anti-TREM2 antibody light chain variable region comprises a sequence that is at least 80% identical, at least 90% identical, at least 95% identical, or at least 98% identical to a sequence selected from SEQ ID NOs: 208-236 and 313-318. In certain embodiments, an isolated nucleic acid encoding an anti-TREM2 antibody light chain variable region comprises a sequence selected from SEQ ID NOs: 208-236 and 313-318. In related embodiments, an isolated nucleic acid encoding an anti-TREM2 antibody heavy chain variable region comprises a sequence that is at least 80% identical, at least 90% identical, at least 95% identical, or at least 98% identical to a sequence selected from SEQ ID NOs: 237-264 and 319-325. In other related embodiments, an isolated nucleic acid encoding an anti-TREM2 antibody heavy chain variable region comprises a sequence selected from SEQ ID NOs: 237-264 and 319-325.

[0197] The nucleic acid sequences provided in Table 6 are exemplary only. As will be appreciated by those in the art, due to the degeneracy of the genetic code, an extremely large

number of nucleic acids may be made, all of which encode the CDRs, variable regions, and heavy and light chains or other components of the antigen binding proteins described herein. Thus, having identified a particular amino acid sequence, those skilled in the art could make any number of different nucleic acids, by simply modifying the sequence of one or more codons in a way which does not change the amino acid sequence of the encoded protein.

[0198] The present invention also includes vectors comprising one or more nucleic acids encoding one or more components of the antigen binding proteins of the invention (e.g. variable regions, light chains, and heavy chains). The term “vector” refers to any molecule or entity (e.g., nucleic acid, plasmid, bacteriophage or virus) used to transfer protein coding information into a host cell. Examples of vectors include, but are not limited to, plasmids, viral vectors, non-episomal mammalian vectors and expression vectors, for example, recombinant expression vectors. The term “expression vector” or “expression construct” as used herein refers to a recombinant DNA molecule containing a desired coding sequence and appropriate nucleic acid control sequences necessary for the expression of the operably linked coding sequence in a particular host cell. An expression vector can include, but is not limited to, sequences that affect or control transcription, translation, and, if introns are present, affect RNA splicing of a coding region operably linked thereto. Nucleic acid sequences necessary for expression in prokaryotes include a promoter, optionally an operator sequence, a ribosome binding site and possibly other sequences. Eukaryotic cells are known to utilize promoters, enhancers, and termination and polyadenylation signals. A secretory signal peptide sequence can also, optionally, be encoded by the expression vector, operably linked to the coding sequence of interest, so that the expressed polypeptide can be secreted by the recombinant host cell, for more facile isolation of the polypeptide of interest from the cell, if desired. For instance, in some embodiments, signal peptide sequences may be appended/fused to the amino terminus of any of the variable region polypeptide sequences listed in Tables 1A, 1B, 2A, 2B, 3A, and 3B. In certain embodiments, a signal peptide having the amino acid sequence of MDMRVPAQLLGLLLLWLRGARC (SEQ ID NO: 265) is fused to the amino terminus of any of the variable region polypeptide sequences in Tables 1A, 1B, 2A, 2B, 3A, and 3B. In other embodiments, a signal peptide having the amino acid sequence of MAWALLLLTLLTQGTGSWA (SEQ ID NO: 266) is fused to the amino terminus of any of the variable region polypeptide sequences in Tables 1A, 1B, 2A, 2B, 3A, and 3B. In still other embodiments, a signal peptide having the amino acid sequence of MTCSPLLLTLLIHCTGSWA (SEQ ID NO: 267) is fused to the amino terminus of any of

the variable region polypeptide sequences in Tables 1A, 1B, 2A, 2B, 3A, and 3B. Other suitable signal peptide sequences that can be fused to the amino terminus of the variable region polypeptide sequences described herein include: MEAPAQLLFLLLLWLPDTTG (SEQ ID NO: 268), MEWTWRVFLVAAATGAHS (SEQ ID NO: 269), METPAQLLFLLLLWLPDTTG (SEQ ID NO: 270), MKHLWFFLLLVAAPRWVLS (SEQ ID NO: 272), MEWSWVFLFFLSVTTGVHS (SEQ ID NO: 273), MDIRAPTQLLGLLLLWLPGAKC (SEQ ID NO: 274), MDIRAPTQLLGLLLLWLPGARC (SEQ ID NO: 275), MDTRAPTQLLGLLLLWLPGATF (SEQ ID NO: 276), MDTRAPTQLLGLLLLWLPGARC (SEQ ID NO: 277), METGLRWLLLVAVLKGVQC (SEQ ID NO: 278), METGLRWLLLVAVLKGVQCQE (SEQ ID NO: 279), and MDMRAPTQLLGLLLLWLPGARC (SEQ ID NO: 280). Other signal or secretory peptides are known to those of skill in the art and may be fused to any of the variable region polypeptide chains listed in Tables 1A, 1B, 2A, 2B, 3A, and 3B, for example, to facilitate or optimize expression in particular host cells.

[0199] Typically, expression vectors used in the host cells to produce the TREM2 agonist antigen binding proteins of the invention will contain sequences for plasmid maintenance and for cloning and expression of exogenous nucleotide sequences encoding the components of the antigen binding proteins. Such sequences, collectively referred to as “flanking sequences,” in certain embodiments will typically include one or more of the following nucleotide sequences: a promoter, one or more enhancer sequences, an origin of replication, a transcriptional termination sequence, a complete intron sequence containing a donor and acceptor splice site, a sequence encoding a leader sequence for polypeptide secretion, a ribosome binding site, a polyadenylation sequence, a polylinker region for inserting the nucleic acid encoding the polypeptide to be expressed, and a selectable marker element. Each of these sequences is discussed below.

[0200] Optionally, the vector may contain a “tag”-encoding sequence, i.e., an oligonucleotide molecule located at the 5' or 3' end of the polypeptide coding sequence; the oligonucleotide tag sequence encodes polyHis (such as hexaHis), FLAG, HA (hemagglutinin influenza virus), myc, or another “tag” molecule for which commercially available antibodies exist. This tag is typically fused to the polypeptide upon expression of the polypeptide, and can serve as a means for affinity purification or detection of the polypeptide from the host cell. Affinity purification can be accomplished, for example, by column chromatography using antibodies

against the tag as an affinity matrix. Optionally, the tag can subsequently be removed from the purified polypeptide by various means such as using certain peptidases for cleavage.

[0201] Flanking sequences may be homologous (i.e., from the same species and/or strain as the host cell), heterologous (i.e., from a species other than the host cell species or strain), hybrid (i.e., a combination of flanking sequences from more than one source), synthetic or native. As such, the source of a flanking sequence may be any prokaryotic or eukaryotic organism, any vertebrate or invertebrate organism, or any plant, provided that the flanking sequence is functional in, and can be activated by, the host cell machinery.

[0202] Flanking sequences useful in the vectors of this invention may be obtained by any of several methods well known in the art. Typically, flanking sequences useful herein will have been previously identified by mapping and/or by restriction endonuclease digestion and can thus be isolated from the proper tissue source using the appropriate restriction endonucleases. In some cases, the full nucleotide sequence of a flanking sequence may be known. Here, the flanking sequence may be synthesized using routine methods for nucleic acid synthesis or cloning.

[0203] Whether all or only a portion of the flanking sequence is known, it may be obtained using polymerase chain reaction (PCR) and/or by screening a genomic library with a suitable probe such as an oligonucleotide and/or flanking sequence fragment from the same or another species. Where the flanking sequence is not known, a fragment of DNA containing a flanking sequence may be isolated from a larger piece of DNA that may contain, for example, a coding sequence or even another gene or genes. Isolation may be accomplished by restriction endonuclease digestion to produce the proper DNA fragment followed by isolation using agarose gel purification, Qiagen® column chromatography (Chatsworth, CA), or other methods known to the skilled artisan. The selection of suitable enzymes to accomplish this purpose will be readily apparent to one of ordinary skill in the art.

[0204] An origin of replication is typically a part of those prokaryotic expression vectors purchased commercially, and the origin aids in the amplification of the vector in a host cell. If the vector of choice does not contain an origin of replication site, one may be chemically synthesized based on a known sequence, and ligated into the vector. For example, the origin of replication from the plasmid pBR322 (New England Biolabs, Beverly, MA) is suitable for most gram-negative bacteria, and various viral origins (e.g., SV40, polyoma, adenovirus, vesicular stomatitis virus (VSV), or papillomaviruses such as HPV or BPV) are useful for cloning vectors in mammalian cells. Generally, the origin of replication component is not

needed for mammalian expression vectors (for example, the SV40 origin is often used only because it also contains the virus early promoter).

[0205] A transcription termination sequence is typically located 3' to the end of a polypeptide coding region and serves to terminate transcription. Usually, a transcription termination sequence in prokaryotic cells is a G-C rich fragment followed by a poly-T sequence. While the sequence is easily cloned from a library or even purchased commercially as part of a vector, it can also be readily synthesized using known methods for nucleic acid synthesis.

[0206] A selectable marker gene encodes a protein necessary for the survival and growth of a host cell grown in a selective culture medium. Typical selection marker genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, tetracycline, or kanamycin for prokaryotic host cells; (b) complement auxotrophic deficiencies of the cell; or (c) supply critical nutrients not available from complex or defined media. Specific selectable markers are the kanamycin resistance gene, the ampicillin resistance gene, and the tetracycline resistance gene. Advantageously, a neomycin resistance gene may also be used for selection in both prokaryotic and eukaryotic host cells.

[0207] Other selectable genes may be used to amplify the gene that will be expressed. Amplification is the process wherein genes that are required for production of a protein critical for growth or cell survival are reiterated in tandem within the chromosomes of successive generations of recombinant cells. Examples of suitable selectable markers for mammalian cells include dihydrofolate reductase (DHFR) and promoterless thymidine kinase genes. Mammalian cell transformants are placed under selection pressure wherein only the transformants are uniquely adapted to survive by virtue of the selectable gene present in the vector. Selection pressure is imposed by culturing the transformed cells under conditions in which the concentration of selection agent in the medium is successively increased, thereby leading to the amplification of both the selectable gene and the DNA that encodes another gene, such as one or more components of the antigen binding proteins described herein. As a result, increased quantities of a polypeptide are synthesized from the amplified DNA.

[0208] A ribosome-binding site is usually necessary for translation initiation of mRNA and is characterized by a Shine-Dalgarno sequence (prokaryotes) or a Kozak sequence (eukaryotes). The element is typically located 3' to the promoter and 5' to the coding sequence of the polypeptide to be expressed. In certain embodiments, one or more coding regions may be

operably linked to an internal ribosome binding site (IRES), allowing translation of two open reading frames from a single RNA transcript.

[0209] In some cases, such as where glycosylation is desired in a eukaryotic host cell expression system, one may manipulate the various pre- or prosequences to improve glycosylation or yield. For example, one may alter the peptidase cleavage site of a particular signal peptide, or add prosequences, which also may affect glycosylation. The final protein product may have, in the -1 position (relative to the first amino acid of the mature protein) one or more additional amino acids incident to expression, which may not have been totally removed. For example, the final protein product may have one or two amino acid residues found in the peptidase cleavage site, attached to the amino-terminus. Alternatively, use of some enzyme cleavage sites may result in a slightly truncated form of the desired polypeptide, if the enzyme cuts at such area within the mature polypeptide.

[0210] Expression and cloning vectors of the invention will typically contain a promoter that is recognized by the host organism and operably linked to the molecule encoding the polypeptide. The term “operably linked” as used herein refers to the linkage of two or more nucleic acid sequences in such a manner that a nucleic acid molecule capable of directing the transcription of a given gene and/or the synthesis of a desired protein molecule is produced. For example, a control sequence in a vector that is “operably linked” to a protein coding sequence is ligated thereto so that expression of the protein coding sequence is achieved under conditions compatible with the transcriptional activity of the control sequences. More specifically, a promoter and/or enhancer sequence, including any combination of cis-acting transcriptional control elements is operably linked to a coding sequence if it stimulates or modulates the transcription of the coding sequence in an appropriate host cell or other expression system.

[0211] Promoters are non-transcribed sequences located upstream (i.e., 5') to the start codon of a structural gene (generally within about 100 to 1000 bp) that control transcription of the structural gene. Promoters are conventionally grouped into one of two classes: inducible promoters and constitutive promoters. Inducible promoters initiate increased levels of transcription from DNA under their control in response to some change in culture conditions, such as the presence or absence of a nutrient or a change in temperature. Constitutive promoters, on the other hand, uniformly transcribe a gene to which they are operably linked, that is, with little or no control over gene expression. A large number of promoters, recognized by a variety of potential host cells, are well known. A suitable promoter is

operably linked to the DNA encoding e.g., heavy chain, light chain, or other component of the antigen binding proteins of the invention, by removing the promoter from the source DNA by restriction enzyme digestion and inserting the desired promoter sequence into the vector.

[0212] Suitable promoters for use with yeast hosts are also well known in the art. Yeast enhancers are advantageously used with yeast promoters. Suitable promoters for use with mammalian host cells are well known and include, but are not limited to, those obtained from the genomes of viruses such as polyoma virus, fowlpox virus, adenovirus (such as Adenovirus serotypes 2, 8 or 9), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, retroviruses, hepatitis-B virus and Simian Virus 40 (SV40). Other suitable mammalian promoters include heterologous mammalian promoters, for example, heat-shock promoters and the actin promoter.

[0213] Additional promoters which may be of interest include, but are not limited to: SV40 early promoter (Benoist and Chambon, 1981, *Nature* 290:304-310); CMV promoter (Thomsen et al., 1984, *Proc. Natl. Acad. U.S.A.* 81:659-663); the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., 1980, *Cell* 22:787-797); herpes thymidine kinase promoter (Wagner et al., 1981, *Proc. Natl. Acad. Sci. U.S.A.* 78: 1444-1445); promoter and regulatory sequences from the metallothioneine gene Prinster et al., 1982, *Nature* 296:39-42); and prokaryotic promoters such as the beta-lactamase promoter (Villa-Kamaroff et al., 1978, *Proc. Natl. Acad. Sci. U.S.A.* 75:3727-3731); or the tac promoter (DeBoer et al., 1983, *Proc. Natl. Acad. Sci. U.S.A.* 80:21-25). Also of interest are the following animal transcriptional control regions, which exhibit tissue specificity and have been utilized in transgenic animals: the elastase I gene control region that is active in pancreatic acinar cells (Swift et al., 1984, *Cell* 38:639-646; Ornitz et al., 1986, *Cold Spring Harbor Symp. Quant. Biol.* 50:399-409; MacDonald, 1987, *Hepatology* 7:425-515); the insulin gene control region that is active in pancreatic beta cells (Hanahan, 1985, *Nature* 315: 115-122); the immunoglobulin gene control region that is active in lymphoid cells (Grosschedl et al., 1984, *Cell* 38:647-658; Adames et al., 1985, *Nature* 318:533-538; Alexander et al., 1987, *Mol. Cell. Biol.* 7: 1436-1444); the mouse mammary tumor virus control region that is active in testicular, breast, lymphoid and mast cells (Leder et al., 1986, *Cell* 45:485-495); the albumin gene control region that is active in liver (Pinkert et al., 1987, *Genes and Devel.* 1:268-276); the alpha-feto-protein gene control region that is active in liver (Krumlauf et al., 1985, *Mol. Cell. Biol.* 5: 1639-1648; Hammer et al., 1987, *Science* 253:53-

58); the alpha 1-antitrypsin gene control region that is active in liver (Kelsey et al., 1987, *Genes and Devel.* 1: 161-171); the beta-globin gene control region that is active in myeloid cells (Mogam et al, 1985, *Nature* 315:338-340; Kollias et al, 1986, *Cell* 46:89-94); the myelin basic protein gene control region that is active in oligodendrocyte cells in the brain (Readhead et al., 1987, *Cell* 48:703-712); the myosin light chain-2 gene control region that is active in skeletal muscle (Sani, 1985, *Nature* 314:283-286); and the gonadotropic releasing hormone gene control region that is active in the hypothalamus (Mason et al., 1986, *Science* 234: 1372-1378).

[0214] An enhancer sequence may be inserted into the vector to increase transcription of DNA encoding a component of the antigen binding proteins (e.g., light chain, heavy chain, or variable regions) by higher eukaryotes. Enhancers are cis-acting elements of DNA, usually about 10-300 bp in length, that act on the promoter to increase transcription. Enhancers are relatively orientation and position independent, having been found at positions both 5' and 3' to the transcription unit. Several enhancer sequences available from mammalian genes are known (e.g., globin, elastase, albumin, alpha-feto-protein and insulin). Typically, however, an enhancer from a virus is used. The SV40 enhancer, the cytomegalovirus early promoter enhancer, the polyoma enhancer, and adenovirus enhancers known in the art are exemplary enhancing elements for the activation of eukaryotic promoters. While an enhancer may be positioned in the vector either 5' or 3' to a coding sequence, it is typically located at a site 5' from the promoter. A sequence encoding an appropriate native or heterologous signal sequence (leader sequence or signal peptide) can be incorporated into an expression vector, to promote extracellular secretion of the antigen binding protein. The choice of signal peptide or leader depends on the type of host cells in which the antigen binding protein is to be produced, and a heterologous signal sequence can replace the native signal sequence. Examples of signal peptides are described above. Other signal peptides that are functional in mammalian host cells include the signal sequence for interleukin-7 (IL-7) described in US Patent No. 4,965,195; the signal sequence for interleukin-2 receptor described in Cosman *et al.*, 1984, *Nature* 312:768; the interleukin-4 receptor signal peptide described in EP Patent No. 0367 566; the type I interleukin-1 receptor signal peptide described in U.S. Patent No. 4,968,607; the type II interleukin-1 receptor signal peptide described in EP Patent No. 0 460 846.

[0215] The expression vectors may be constructed from a starting vector such as a commercially available vector. Such vectors may or may not contain all of the desired

flanking sequences. Where one or more of the flanking sequences described herein are not already present in the vector, they may be individually obtained and ligated into the vector. Methods used for obtaining each of the flanking sequences are well known to one skilled in the art. The expression vectors can be introduced into host cells to thereby produce proteins, including fusion proteins, encoded by nucleic acids as described herein.

[0216] In certain embodiments, nucleic acids encoding the different components of the TREM2 agonist antigen binding proteins of the invention may be inserted into the same expression vector. For instance, the nucleic acid encoding an anti-TREM2 antibody light chain or variable region can be cloned into the same vector as the nucleic acid encoding an anti-TREM2 antibody heavy chain or variable region. In such embodiments, the two nucleic acids may be separated by an internal ribosome entry site (IRES) and under the control of a single promoter such that the light chain and heavy chain are expressed from the same mRNA transcript. Alternatively, the two nucleic acids may be under the control of two separate promoters such that the light chain and heavy chain are expressed from two separate mRNA transcripts. In some embodiments, the nucleic acid encoding the anti-TREM2 antibody light chain or variable region is cloned into one expression vector and the nucleic acid encoding the anti-TREM2 antibody heavy chain or variable region is cloned into a second expression vector. In such embodiments, a host cell may be co-transfected with both expression vectors to produce complete antigen binding proteins of the invention.

[0217] After the vector has been constructed and the one or more nucleic acid molecules encoding the components of the antigen binding proteins described herein has been inserted into the proper site(s) of the vector or vectors, the completed vector(s) may be inserted into a suitable host cell for amplification and/or polypeptide expression. Thus, the present invention encompasses an isolated host cell or cell line comprising one or more expression vectors encoding the components of the TREM2 agonist antigen binding proteins described herein. The term "host cell" as used herein refers to a cell that has been transformed, or is capable of being transformed, with a nucleic acid and thereby expresses a gene of interest. The term includes the progeny of the parent cell, whether or not the progeny is identical in morphology or in genetic make-up to the original parent cell, so long as the gene of interest is present. A host cell that comprises an isolated nucleic acid of the invention, preferably operably linked to at least one expression control sequence (e.g. promoter or enhancer), is a "recombinant host cell."

[0218] The transformation of an expression vector for an antigen binding protein into a selected host cell may be accomplished by well-known methods including transfection, infection, calcium phosphate co-precipitation, electroporation, microinjection, lipofection, DEAE-dextran mediated transfection, or other known techniques. The method selected will in part be a function of the type of host cell to be used. These methods and other suitable methods are well known to the skilled artisan, and are set forth, for example, in Sambrook *et al.*, 2001.

[0219] A host cell, when cultured under appropriate conditions, synthesizes an antigen binding protein that can subsequently be collected from the culture medium (if the host cell secretes it into the medium) or directly from the host cell producing it (if it is not secreted). The selection of an appropriate host cell will depend upon various factors, such as desired expression levels, polypeptide modifications that are desirable or necessary for activity (such as glycosylation or phosphorylation) and ease of folding into a biologically active molecule.

[0220] Exemplary host cells include prokaryote, yeast, or higher eukaryote cells. Prokaryotic host cells include eubacteria, such as Gram-negative or Gram-positive organisms, for example, *Enterobacteriaceae* such as *Escherichia*, e.g., *E. coli*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella*, e.g., *Salmonella typhimurium*, *Serratia*, e.g., *Serratia marcescans*, and *Shigella*, as well as *Bacillus*, such as *B. subtilis* and *B. licheniformis*, *Pseudomonas*, and *Streptomyces*. Eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for recombinant polypeptides. *Saccharomyces cerevisiae*, or common baker's yeast, is the most commonly used among lower eukaryotic host microorganisms. However, a number of other genera, species, and strains are commonly available and useful herein, such as *Pichia*, e.g. *P. pastoris*, *Schizosaccharomyces pombe*; *Kluyveromyces*, *Yarrowia*; *Candida*; *Trichoderma reesia*; *Neurospora crassa*; *Schwanniomyces*, such as *Schwanniomyces occidentalis*; and filamentous fungi, such as, e.g., *Neurospora*, *Penicillium*, *Tolypocladium*, and *Aspergillus* hosts such as *A. nidulans* and *A. niger*.

[0221] Host cells for the expression of glycosylated antigen binding proteins can be derived from multicellular organisms. Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts such as *Spodoptera frugiperda* (caterpillar), *Aedes aegypti* (mosquito), *Aedes albopictus* (mosquito), *Drosophila melanogaster* (fruitfly), and *Bombyx mori* have been

identified. A variety of viral strains for transfection of such cells are publicly available, e.g., the L-1 variant of *Autographa californica* NPV and the Bm-5 strain of *Bombyx mori* NPV.

[0222] Vertebrate host cells are also suitable hosts, and recombinant production of antigen binding proteins from such cells has become routine procedure. Mammalian cell lines available as hosts for expression are well known in the art and include, but are not limited to, immortalized cell lines available from the American Type Culture Collection (ATCC), including but not limited to Chinese hamster ovary (CHO) cells, including CHOK1 cells (ATCC CCL61), DXB-11, DG-44, and Chinese hamster ovary cells/-DHFR (CHO, Urlaub *et al.*, Proc. Natl. Acad. Sci. USA 77: 4216, 1980); monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, (Graham *et al.*, J. Gen Virol. 36: 59, 1977); baby hamster kidney cells (BHK, ATCC CCL 10); mouse sertoli cells (TM4, Mather, Biol. Reprod. 23: 243-251, 1980); monkey kidney cells (CV1 ATCC CCL 70); African green monkey kidney cells (VERO-76, ATCC CRL-1587); human cervical carcinoma cells (HELA, ATCC CCL 2); canine kidney cells (MDCK, ATCC CCL 34); buffalo rat liver cells (BRL 3A, ATCC CRL 1442); human lung cells (W138, ATCC CCL 75); human hepatoma cells (Hep G2, HB 8065); mouse mammary tumor (MMT 060562, ATCC CCL51); TRI cells (Mather *et al.*, Annals N.Y Acad. Sci. 383: 44-68, 1982); MRC 5 cells or FS4 cells; mammalian myeloma cells, and a number of other cell lines. In certain embodiments, cell lines may be selected through determining which cell lines have high expression levels and constitutively produce antigen binding proteins with human TREM2 binding properties. In another embodiment, a cell line from the B cell lineage that does not make its own antibody but has a capacity to make and secrete a heterologous antibody can be selected. CHO cells are preferred host cells in some embodiments for expressing the TREM2 agonist antigen binding proteins of the invention.

[0223] Host cells are transformed or transfected with the above-described nucleic acids or vectors for production of TREM2 agonist antigen binding proteins and are cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. In addition, novel vectors and transfected cell lines with multiple copies of transcription units separated by a selective marker are particularly useful for the expression of antigen binding proteins. Thus, the present invention also provides a method for producing a TREM2 agonist antigen binding protein described herein, such as an anti-TREM2 agonist monoclonal antibody or binding

fragment thereof, comprising culturing a host cell comprising one or more expression vectors described herein in a culture medium under conditions permitting expression of the antigen binding protein encoded by the one or more expression vectors; and recovering the antigen binding protein from the culture medium or host cell.

[0224] The host cells used to produce the antigen binding proteins of the invention may be cultured in a variety of media. Commercially available media such as Ham's F10 (Sigma), Minimal Essential Medium (MEM, Sigma), RPMI-1640 (Sigma), and Dulbecco's Modified Eagle's Medium (DMEM, Sigma) are suitable for culturing the host cells. In addition, any of the media described in Ham *et al.*, Meth. Enz. 58: 44, 1979; Barnes *et al.*, Anal. Biochem. 102: 255, 1980; U.S. Patent Nos. 4,767,704; 4,657,866; 4,927,762; 4,560,655; or 5,122,469; WO90103430; WO 87/00195; or U.S. Patent Re. No. 30,985 may be used as culture media for the host cells. Any of these media may be supplemented as necessary with hormones and/or other growth factors (such as insulin, transferrin, or epidermal growth factor), salts (such as sodium chloride, calcium, magnesium, and phosphate), buffers (such as HEPES), nucleotides (such as adenosine and thymidine), antibiotics (such as Gentamycin™ drug), trace elements (defined as inorganic compounds usually present at final concentrations in the micromolar range), and glucose or an equivalent energy source. Any other necessary supplements may also be included at appropriate concentrations that would be known to those skilled in the art. The culture conditions, such as temperature, pH, and the like, are those previously used with the host cell selected for expression, and will be apparent to the ordinary skilled artisan.

[0225] Upon culturing the host cells, the antigen binding protein can be produced intracellularly, in the periplasmic space, or directly secreted into the medium. If the antigen binding protein is produced intracellularly, as a first step, the particulate debris, either host cells or lysed fragments, is removed, for example, by centrifugation or ultrafiltration. The antigen binding protein can be purified using, for example, hydroxyapatite chromatography, cation or anion exchange chromatography, size-exclusion chromatography, or preferably affinity chromatography, using the antigen(s) of interest or protein A or protein G as an affinity ligand. Protein A can be used to purify proteins that include polypeptides that are based on human immunoglobulin $\gamma 1$, $\gamma 2$, or $\gamma 4$ heavy chains (Lindmark *et al.*, J. Immunol. Meth. 62: 1-13, 1983). Protein G is recommended for all mouse isotypes and for human immunoglobulin $\gamma 3$ (Guss *et al.*, EMBO J. 5: 1567-1575, 1986). The matrix to which the affinity ligand is attached is most often agarose, but other matrices are available.

Mechanically stable matrices such as controlled pore glass or poly(styrene-divinyl)benzene allow for faster flow rates and shorter processing times than can be achieved with agarose. Where the protein comprises a CH3 domain, the Bakerbond ABX™ resin (J. T. Baker, Phillipsburg, N.J.) is useful for purification. Other techniques for protein purification such as ethanol precipitation, Reverse Phase HPLC, chromatofocusing, SDS-PAGE, and ammonium sulfate precipitation are also possible depending on the particular antigen binding protein to be recovered.

[0226] In certain embodiments, the invention provides a composition (e.g. a pharmaceutical composition) comprising one or a plurality of the TREM2 agonist antigen binding proteins of the invention (e.g. anti-TREM2 agonist monoclonal antibodies or binding fragments thereof) together with pharmaceutically acceptable diluents, carriers, excipients, solubilizers, emulsifiers, preservatives, and/or adjuvants. Pharmaceutical compositions of the invention include, but are not limited to, liquid, frozen, and lyophilized compositions.

“Pharmaceutically-acceptable” refers to molecules, compounds, and compositions that are non-toxic to human recipients at the dosages and concentrations employed and/or do not produce allergic or adverse reactions when administered to humans. In some embodiments, the pharmaceutical composition may contain formulation materials for modifying, maintaining or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. In such embodiments, suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen-sulfite); buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates or other organic acids); bulking agents (such as mannitol or glycine); chelating agents (such as ethylenediamine tetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin); fillers; monosaccharides; disaccharides; and other carbohydrates (such as glucose, mannose or dextrans); proteins (such as serum albumin, gelatin or immunoglobulins); coloring, flavoring and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counterions (such as sodium); preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide); solvents (such as glycerin, propylene glycol or polyethylene glycol);

sugar alcohols (such as mannitol or sorbitol); suspending agents; surfactants or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate 80, triton, tromethamine, lecithin, cholesterol, tyloxapal); stability enhancing agents (such as sucrose or sorbitol); tonicity enhancing agents (such as alkali metal halides, preferably sodium or potassium chloride, mannitol sorbitol); delivery vehicles; diluents; excipients and/or pharmaceutical adjuvants. Methods and suitable materials for formulating molecules for therapeutic use are known in the pharmaceutical arts, and are described, for example, in REMINGTON'S PHARMACEUTICAL SCIENCES, 18th Edition, (A.R. Genrmo, ed.), 1990, Mack Publishing Company.

[0227] In some embodiments, the pharmaceutical composition of the invention comprises a standard pharmaceutical carrier, such as a sterile phosphate buffered saline solution, bacteriostatic water, and the like. A variety of aqueous carriers may be used, e.g., water, buffered water, 0.4% saline, 0.3% glycine and the like, and may include other proteins for enhanced stability, such as albumin, lipoprotein, globulin, etc., subjected to mild chemical modifications or the like.

[0228] Exemplary concentrations of the antigen binding proteins in the formulation may range from about 0.1 mg/ml to about 200 mg/ml or from about 0.1 mg/mL to about 50 mg/mL, or from about 0.5 mg/mL to about 25 mg/mL, or alternatively from about 2 mg/mL to about 10 mg/mL. An aqueous formulation of the antigen binding protein may be prepared in a pH-buffered solution, for example, at pH ranging from about 4.5 to about 6.5, or from about 4.8 to about 5.5, or alternatively about 5.0. Examples of buffers that are suitable for a pH within this range include acetate (e.g. sodium acetate), succinate (such as sodium succinate), gluconate, histidine, citrate and other organic acid buffers. The buffer concentration can be from about 1 mM to about 200 mM, or from about 10 mM to about 60 mM, depending, for example, on the buffer and the desired isotonicity of the formulation.

[0229] A tonicity agent, which may also stabilize the antigen binding protein, may be included in the formulation. Exemplary tonicity agents include polyols, such as mannitol, sucrose or trehalose. Preferably the aqueous formulation is isotonic, although hypertonic or hypotonic solutions may be suitable. Exemplary concentrations of the polyol in the formulation may range from about 1% to about 15% w/v.

[0230] A surfactant may also be added to the antigen binding protein formulation to reduce aggregation of the formulated antigen binding protein and/or minimize the formation of particulates in the formulation and/or reduce adsorption. Exemplary surfactants include

nonionic surfactants such as polysorbates (e.g. polysorbate 20 or polysorbate 80) or poloxamers (e.g. poloxamer 188). Exemplary concentrations of surfactant may range from about 0.001% to about 0.5%, or from about 0.005% to about 0.2%, or alternatively from about 0.004% to about 0.01% w/v.

[0231] In one embodiment, the formulation contains the above-identified agents (i.e. antigen binding protein, buffer, polyol and surfactant) and is essentially free of one or more preservatives, such as benzyl alcohol, phenol, m-cresol, chlorobutanol and benzethonium chloride. In another embodiment, a preservative may be included in the formulation, e.g., at concentrations ranging from about 0.1% to about 2%, or alternatively from about 0.5% to about 1%. One or more other pharmaceutically acceptable carriers, excipients or stabilizers such as those described in REMINGTON'S PHARMACEUTICAL SCIENCES, 18th Edition, (A.R. Genrmo, ed.), 1990, Mack Publishing Company, may be included in the formulation provided that they do not adversely affect the desired characteristics of the formulation.

[0232] Therapeutic formulations of the antigen binding protein are prepared for storage by mixing the antigen binding protein having the desired degree of purity with optional physiologically acceptable carriers, excipients or stabilizers (REMINGTON'S PHARMACEUTICAL SCIENCES, 18th Edition, (A.R. Genrmo, ed.), 1990, Mack Publishing Company), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers (e.g. phosphate, citrate, and other organic acids); antioxidants (e.g. ascorbic acid and methionine); preservatives (such as octadecyldimethylbenzyl ammonium chloride, hexamethonium chloride, benzalkonium chloride, benzethonium chloride, phenol, butyl or benzyl alcohol, alkyl parabens such as methyl or propyl paraben, catechol; resorcinol, cyclohexanol, 3-pentanol, and m-cresol); low molecular weight (e.g. less than about 10 residues) polypeptides; proteins (such as serum albumin, gelatin, or immunoglobulins); hydrophilic polymers (e.g. polyvinylpyrrolidone); amino acids (e.g. glycine, glutamine, asparagine, histidine, arginine, or lysine); monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, maltose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants, such as polysorbates (e.g. polysorbate 20 or polysorbate 80) or poloxamers (e.g. poloxamer 188); or polyethylene glycol (PEG).

[0233] In one embodiment, a suitable formulation of the claimed invention contains an isotonic buffer such as a phosphate, acetate, or TRIS buffer in combination with a tonicity agent, such as a polyol, sorbitol, sucrose or sodium chloride, which tonicifies and stabilizes. One example of such a tonicity agent is 5% sorbitol or sucrose. In addition, the formulation could optionally include a surfactant at 0.01% to 0.02% wt/vol, for example, to prevent aggregation or improve stability. The pH of the formulation may range from 4.5 to 6.5 or 4.5 to 5.5. Other exemplary descriptions of pharmaceutical formulations for antigen binding proteins may be found in US Patent Publication No. 2003/0113316 and US Patent No. 6,171,586, each of which is hereby incorporated by reference in its entirety.

[0234] Suspensions and crystal forms of antigen binding proteins are also contemplated. Methods to make suspensions and crystal forms are known to one of skill in the art.

[0235] The formulations to be used for *in vivo* administration must be sterile. The compositions of the invention may be sterilized by conventional, well-known sterilization techniques. For example, sterilization is readily accomplished by filtration through sterile filtration membranes. The resulting solutions may be packaged for use or filtered under aseptic conditions and lyophilized, the lyophilized preparation being combined with a sterile solution prior to administration.

[0236] The process of freeze-drying is often employed to stabilize polypeptides for long-term storage, particularly when the polypeptide is relatively unstable in liquid compositions. A lyophilization cycle is usually composed of three steps: freezing, primary drying, and secondary drying (*see* Williams and Polli, *Journal of Parenteral Science and Technology*, Volume 38, Number 2, pages 48-59, 1984). In the freezing step, the solution is cooled until it is adequately frozen. Bulk water in the solution forms ice at this stage. The ice sublimates in the primary drying stage, which is conducted by reducing chamber pressure below the vapor pressure of the ice, using a vacuum. Finally, sorbed or bound water is removed at the secondary drying stage under reduced chamber pressure and an elevated shelf temperature. The process produces a material known as a lyophilized cake. Thereafter the cake can be reconstituted prior to use.

[0237] The standard reconstitution practice for lyophilized material is to add back a volume of pure water (typically equivalent to the volume removed during lyophilization), although dilute solutions of antibacterial agents are sometimes used in the production of pharmaceuticals for parenteral administration (*see* Chen, *Drug Development and Industrial Pharmacy*, Volume 18: 1311-1354, 1992).

[0238] Excipients have been noted in some cases to act as stabilizers for freeze-dried products (*see* Carpenter *et al.*, Volume 74: 225-239, 1991). For example, known excipients include polyols (including mannitol, sorbitol and glycerol); sugars (including glucose and sucrose); and amino acids (including alanine, glycine and glutamic acid).

[0239] In addition, polyols and sugars are also often used to protect polypeptides from freezing and drying-induced damage and to enhance the stability during storage in the dried state. In general, sugars, in particular disaccharides, are effective in both the freeze-drying process and during storage. Other classes of molecules, including mono- and di-saccharides and polymers such as PVP, have also been reported as stabilizers of lyophilized products.

[0240] For injection, the pharmaceutical formulation and/or medicament may be a powder suitable for reconstitution with an appropriate solution as described above. Examples of these include, but are not limited to, freeze dried, rotary dried or spray dried powders, amorphous powders, granules, precipitates, or particulates. For injection, the formulations may optionally contain stabilizers, pH modifiers, surfactants, bioavailability modifiers and combinations of these.

[0241] Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antigen binding protein, which matrices are in the form of shaped articles, e.g., films, or microcapsule. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Patent No. 3,773,919), copolymers of L-glutamic acid and γ ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the Lupron Depot™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated polypeptides remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic

solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

[0242] The formulations of the invention may be designed to be short-acting, fast-releasing, long-acting, or sustained-releasing. Thus, the pharmaceutical formulations may also be formulated for controlled release or for slow release.

[0243] Specific dosages may be adjusted depending on the disease, disorder, or condition to be treated (e.g. Alzheimer's disease, multiple sclerosis, frontotemporal dementia, or Nasu-Hakola disease), the age, body weight, general health conditions, sex, and diet of the subject, dose intervals, administration routes, excretion rate, and combinations of drugs.

[0244] The TREM2 agonist antigen binding proteins of the invention can be administered by any suitable means, including parenteral, subcutaneous, intraperitoneal, intrapulmonary, intrathecal, intracerebral, intracerebroventricular, and intranasal, and, if desired for local treatment, intralesional administration. Parenteral administration includes intravenous, intraarterial, intraperitoneal, intramuscular, intradermal or subcutaneous administration. In addition, the antigen binding protein is suitably administered by pulse infusion, particularly with declining doses of the antigen binding protein. Preferably, the dosing is given by injections, most preferably intravenous or subcutaneous injections, depending in part on whether the administration is brief or chronic. Other administration methods are contemplated, including topical, particularly transdermal, transmucosal, rectal, oral or local administration e.g. through a catheter placed close to the desired site. In certain embodiments, the TREM2 agonist antigen binding protein of the invention is administered intravenously or subcutaneously in a physiological solution at a dose ranging between 0.01 mg/kg to 100 mg/kg at a frequency ranging from daily to weekly to monthly (e.g. every day, every other day, every third day, or 2, 3, 4, 5, or 6 times per week), preferably a dose ranging from 0.1 to 45 mg/kg, 0.1 to 15 mg/kg or 0.1 to 10 mg/kg at a frequency of once per week, once every two weeks, or once a month.

[0245] The TREM2 agonist antigen binding proteins described herein (e.g. anti-TREM2 agonist monoclonal antibodies and binding fragments thereof) are useful for preventing, treating, or ameliorating a condition associated with TREM2 deficiency or loss of biological function of TREM2 in a patient in need thereof. As used herein, the term "treating" or "treatment" is an intervention performed with the intention of preventing the development or altering the pathology of a disorder. Accordingly, "treatment" refers to both therapeutic treatment and prophylactic or preventative measures. Patients in need of treatment include

those already diagnosed with or suffering from the disorder or condition as well as those in which the disorder or condition is to be prevented, such as patients who are at risk of developing the disorder or condition based on, for example, genetic markers. “Treatment” includes any indicia of success in the amelioration of an injury, pathology or condition, including any objective or subjective parameter such as abatement, remission, diminishing of symptoms, or making the injury, pathology or condition more tolerable to the patient, slowing in the rate of degeneration or decline, making the final point of degeneration less debilitating, or improving a patient’s physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters, including the results of a physical examination, self-reporting by a patient, cognitive tests, motor function tests, neuropsychiatric exams, and/or a psychiatric evaluation.

[0246] TREM2 biological activity has been implicated in various physiological processes, including myeloid cell processes, such as phagocytosis, proliferation, survival, and regulation of inflammatory cytokine production; osteoclastogenesis; osteoclast differentiation; negative regulation of autoimmunity; inflammatory responses; bone remodeling and repair; bone resorption; tissue repair, microgliosis, and brain homeostasis. *See, e.g.*, Colonna, *Nature Reviews Immunology*, Vol. 3: 445-453, 2003; Paradowska-Gorycka *et al.*, *Human Immunology*, Vol. 74: 730-737, 2013; and Ulrich and Holtzman, *ACS Chem. Neurosci.*, Vol. 7: 420-427, 2016. Loss of TREM2 function or TREM2 deficiency has been linked to several disorders and diseases including polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOS; also known as Nasu-Hakola disease), Alzheimer’s disease, frontotemporal dementia, multiple sclerosis, prion disease, stroke, osteoporosis, and osteopetrosis. *See, e.g.*, Jonsson *et al.*, *New England Journal of Medicine*, Vol. 368: 107-116, 2013; Guerreiro *et al.*, *New England Journal of Medicine*, Vol. 368: 117-127, 2013; Paradowska-Gorycka *et al.*, *Human Immunology*, Vol. 74: 730-737, 2013; and Ulrich and Holtzman, *ACS Chem. Neurosci.*, Vol. 7: 420-427, 2016. Thus, the TREM2 agonist antigen binding proteins of the invention can be administered to patients to prevent, ameliorate, or treat any of these diseases or disorders or other conditions associated with TREM2 deficiency or loss of TREM2 biological function or activity. In certain embodiments, the present invention provides methods for preventing, treating, or ameliorating a condition associated with TREM2 deficiency or loss of TREM2 function in a patient in need thereof comprising administering to the patient an effective amount of a TREM2 agonist antigen binding protein described herein. In certain embodiments, the TREM2 agonist antigen binding protein is an

anti-TREM2 agonist monoclonal antibody or binding fragment thereof. The term “patient” includes human patients and is used interchangeably with the term “subject.”

[0247] An “effective amount” is generally an amount sufficient to reduce the severity and/or frequency of symptoms, eliminate the symptoms and/or underlying cause, prevent the occurrence of symptoms and/or their underlying cause, and/or improve or remediate the damage that results from or is associated with a particular condition. In some embodiments, the effective amount is a therapeutically effective amount or a prophylactically effective amount. A “therapeutically effective amount” is an amount sufficient to remedy a disease state or symptom(s), particularly a state or symptom(s) associated with the disease state, or otherwise prevent, hinder, retard or reverse the progression of the disease state or any other undesirable symptom associated with the disease in any way whatsoever (i.e. that provides “therapeutic efficacy”). A “prophylactically effective amount” is an amount of antigen binding protein, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of the condition, or reducing the likelihood of the onset (or reoccurrence) of the condition. The full therapeutic or prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a therapeutically or prophylactically effective amount may be administered in one or more administrations.

[0248] Conditions or disorders associated with TREM2 deficiency or loss of TREM2 function that may be prevented, treated, or ameliorated according to the methods of the invention include, but are not limited to, Nasu-Hakola disease, Alzheimer’s disease, frontotemporal dementia, multiple sclerosis, Guillain-Barre syndrome, amyotrophic lateral sclerosis, Parkinson’s disease, traumatic brain injury, spinal cord injury, systemic lupus erythematosus, rheumatoid arthritis, prion disease, stroke, osteoporosis, osteopetrosis, and osteosclerosis. In certain embodiments, the condition or disorder to be prevented, treated, or ameliorated according to the methods of the invention is Alzheimer’s disease, Nasu-Hakola disease, frontotemporal dementia, multiple sclerosis, prion disease, or stroke.

[0249] In one embodiment, the present invention provides a method for preventing, treating, or ameliorating Alzheimer’s disease in a patient in need thereof comprising administering to the patient an effective amount of a TREM2 agonist antigen binding protein described herein. In certain embodiments, the TREM2 agonist antigen binding protein administered to the patient is an anti-TREM2 agonist monoclonal antibody, such as the antibodies whose variable and CDR sequences are set forth in Tables 1A, 1B, 2A, 2B, 3A, and 3B. In some

embodiments, the patient to be administered a TREM2 agonist antigen binding protein is a patient at risk of developing Alzheimer's disease. For instance, in one embodiment, the patient has been determined to have at least one allele containing the rs75932628-T mutation in the *TREM2* gene, e.g. the patient has a genotype of CT at rs75932628. In related embodiments, the patient at risk of developing Alzheimer's disease is a patient who has been determined to carry a TREM2 variant allele that encodes a histidine in place of arginine at position 47 in SEQ ID NO: 1. In other embodiments, the patient has been determined to have at least one allele containing the rs143332484-T mutation in the *TREM2* gene, e.g. the patient has a genotype of CT at rs143332484. In related embodiments, the patient at risk of developing Alzheimer's disease is a patient who has been determined to carry a TREM2 variant allele that encodes a histidine in place of arginine at position 62 in SEQ ID NO: 1. In some embodiments, a patient at risk of developing Alzheimer's disease has been determined to have at least one allele containing the rs6910730-G mutation in the *TREM1* gene, at least one allele containing the rs7759295-C mutation upstream of the *TREM2* gene, and/or at least one ϵ 4 allele of the *APOE* gene.

[0250] In another embodiment, the present invention provides a method for preventing, treating, or ameliorating frontotemporal dementia or Nasu-Hakola disease in a patient in need thereof comprising administering to the patient an effective amount of a TREM2 agonist antigen binding protein described herein. In certain embodiments, the TREM2 agonist antigen binding protein administered to the patient is an anti-TREM2 agonist monoclonal antibody, such as the antibodies whose variable and CDR sequences are set forth in Tables 1A, 1B, 2A, 2B, 3A, and 3B. In some embodiments, the patient to be administered a TREM2 agonist antigen binding protein is a patient at risk of developing frontotemporal dementia or Nasu-Hakola disease. For example, in one such embodiment, the patient has been determined to have at least one allele containing the rs104894002-A mutation in the *TREM2* gene, e.g. the patient has a genotype of GA or AA at rs104894002. In related embodiments, the patient at risk of developing frontotemporal dementia or Nasu-Hakola disease is a patient who has been determined to carry a TREM2 variant allele that encodes a truncated TREM2 protein as a result of the substitution of a stop codon in place of glutamine at position 33 in SEQ ID NO: 1. In another embodiment, the patient has been determined to have at least one allele containing the rs201258663-A mutation in the *TREM2* gene, e.g. the patient has a genotype of GA or AA at rs201258663. In related embodiments, the patient at risk of developing frontotemporal dementia or Nasu-Hakola disease is a patient who has been determined to

carry a TREM2 variant allele that encodes a methionine in place of threonine at position 66 in SEQ ID NO: 1. In some embodiments, the patient at risk of developing frontotemporal dementia or Nasu-Hakola disease is a patient who has been determined to carry a TREM2 variant allele that encodes a cysteine in place of tyrosine at position 38 in SEQ ID NO: 1.

[0251] In yet another embodiment, the present invention provides a method for preventing, treating, or ameliorating multiple sclerosis in a patient in need thereof comprising administering to the patient an effective amount of a TREM2 agonist antigen binding protein described herein. In certain embodiments, the TREM2 agonist antigen binding protein administered to the patient is an anti-TREM2 agonist monoclonal antibody, such as the antibodies whose variable and CDR sequences are set forth in Tables 1A, 1B, 2A, 2B, 3A, and 3B. In some embodiments, the patient to be administered a TREM2 agonist antigen binding protein is a patient at risk of developing multiple sclerosis.

[0252] As described in Examples 9 and 10, an agonist anti-TREM2 antibody capable of activating TREM2/DAP12 signaling as measured by increases in pSyk levels rescued the viability defect from macrophages and microglia resulting from a loss of function mutation in TREM2 and restored CCL2 secretion from TREM2-deficient macrophages. These results indicate that activation of TREM2/DAP12 signaling with an agonist anti-TREM2 antibody can enhance macrophage/microglia function, which in turn could be therapeutic in conditions associated with insufficient macrophage/microglia function. Thus, in certain embodiments, the present invention includes a method of increasing survival or proliferation of myeloid cells, such as microglia, macrophages, or dendritic cells, in a patient in need thereof comprising administering to the patient an effective amount of a TREM2 agonist antigen binding protein described herein. In certain embodiments, the TREM2 agonist antigen binding protein administered to the patient is an anti-TREM2 agonist monoclonal antibody, such as the antibodies whose variable and CDR sequences are set forth in Tables 1A, 1B, 2A, 2B, 3A, and 3B. In some embodiments, the patient in need of treatment is at risk for, suffers from, or has been diagnosed with a neurodegenerative disorder. In one embodiment, the neurodegenerative disorder is Alzheimer's disease. In some embodiments, the patient in need of treatment is at risk for, suffers from, or has been diagnosed with an autoimmune disorder. In one embodiment, the autoimmune disorder is multiple sclerosis.

[0253] The TREM2 agonist antigen binding proteins of the invention are also useful for detecting human TREM2 in biological samples and identification of cells or tissues that express human TREM2. For instance, the antigen binding proteins can be used in diagnostic

assays, *e.g.*, immunoassays to detect and/or quantify TREM2 expressed in a tissue or cell (macrophages or microglia) or presence of soluble forms of TREM2 in a bodily fluid, such as cerebrospinal fluid, blood, serum, or plasma. In addition, the TREM2 agonist antigen binding proteins described herein can be used to activate TREM2/DAP12 signaling in myeloid cells, thereby modulating the biological activity of these cells. Such biological activities include cytokine release, phagocytosis, and microgliosis.

[0254] The TREM2 agonist antigen binding proteins described herein can be used for diagnostic purposes to detect, diagnose, or monitor conditions associated with TREM2 dysfunction, such as neurodegenerative diseases (*e.g.* Alzheimer's disease, Parkinson's disease), central nervous system injury (traumatic brain injury, spinal cord injury, stroke), autoimmune diseases (multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus), frontotemporal dementia, Nasu-Hakola disease, and bone disorders (*e.g.* osteoporosis, osteopetrosis, osteosclerosis). For instance, elevation in the level of a soluble form of TREM2 in cerebrospinal fluid has been observed in patients with multiple sclerosis (Piccio *et al.*, Brain, Vol. 131: 3081-3091, 2008). Also provided are methods for the detection of the presence of TREM2 in a sample using classical immunohistological methods known to those of skill in the art (*e.g.*, Tijssen, 1993, Practice and Theory of Enzyme Immunoassays, Vol 15 (Eds R.H. Burdon and P.H. van Knippenberg, Elsevier, Amsterdam); Zola, 1987, Monoclonal Antibodies: A Manual of Techniques, pp. 147-158 (CRC Press, Inc.); Jalkanen *et al.*, 1985, J. Cell. Biol. 101:976-985; Jalkanen *et al.*, 1987, J. Cell Biol. 105:3087-3096). Examples of methods useful in the detection of the presence of TREM2 include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA), using the antigen binding proteins described herein. The detection of TREM2 can be performed *in vivo* or *in vitro*.

[0255] For diagnostic applications, the antigen binding protein can be labeled with a detectable labeling group. Suitable labeling groups include, but are not limited to, the following: radioisotopes or radionuclides (*e.g.*, ³H, ¹⁴C, ¹⁵N, ³⁵S, ⁹⁰Y, ⁹⁹Tc, ¹¹¹In, ¹²⁵I, ¹³¹I), fluorescent groups (*e.g.*, FITC, rhodamine, lanthanide phosphors), enzymatic groups (*e.g.*, horseradish peroxidase, β -galactosidase, luciferase, alkaline phosphatase), chemiluminescent groups, biotinyl groups, or predetermined polypeptide epitopes recognized by a secondary reporter (*e.g.*, leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In some embodiments, the labeling group is coupled to the

antigen binding protein via spacer arms of various lengths to reduce potential steric hindrance. Various methods for labeling proteins are known in the art and may be used.

[0256] In another embodiment, the antigen binding proteins described herein can be used to identify a cell or cells that express TREM2. In a specific embodiment, the antigen binding protein is labeled with a labeling group and the binding of the labeled antigen binding protein to TREM2 is detected. The antigen binding proteins can also be used in immunoprecipitation assays in biological samples. In a further specific embodiment, the binding of the antigen binding protein to TREM2 is detected *in vivo*. In a further specific embodiment, the antigen binding protein is isolated and measured using techniques known in the art. *See*, for example, Harlow and Lane, 1988, *Antibodies: A Laboratory Manual*, New York: Cold Spring Harbor (ed. 1991 and periodic supplements); John E. Coligan, ed., 1993, *Current Protocols In Immunology* New York: John Wiley & Sons.

[0257] The following examples, including the experiments conducted and the results achieved, are provided for illustrative purposes only and are not to be construed as limiting the scope of the appended claims.

EXAMPLES

Example 1. Generation of Human Anti-TREM2 Antibodies

Immunizations

[0258] Fully human antibodies to human TREM2 were generated by immunizing XenoMouse® transgenic mice. These transgenic mice carry human immunoglobulin transgenes that allow for production of antigen-specific fully human antibodies upon immunization. *See, e.g.*, U.S. Pat. Nos. 6,114,598; 6,162,963; 6,833,268; 7,049,426; 7,064,244; Green *et al.*, 1994, *Nature Genetics* 7:13-21; Mendez *et al.*, 1997, *Nature Genetics* 15:146-156; Green and Jakobovitis, 1998, *J. Ex. Med.*, 188:483-495; Green, 1999, *Journal of Immunological Methods* 231:11-23; Kellerman and Green, *Current Opinion in Biotechnology* 13, 593-597, 2002, all of which are hereby incorporated by reference in their entireties. Animals from the XMG2-K, XMG2-KL, XMG4-K and XMG4-KL XenoMouse® strains were used for immunizations. Mice of the XenoMouse® strains XMG2-K and XMG2-KL produce fully human IgG2 antibodies with kappa light chains (XMG2-K) or both kappa and lambda light chains (XMG2-KL). Mice of the XenoMouse® strains XMG4-K and XMG4-KL produce fully human IgG4 antibodies with kappa light chains (XMG4-K) or both kappa and lambda light chains (XMG4-KL).

[0259] Multiple immunogens and routes of immunization were used to produce an immune response to human TREM2 in the XenoMouse® strains. For soluble recombinant protein immunizations, mice were immunized with a soluble TREM2 protein, which was a fusion protein comprising the extracellular domain (ECD) of human TREM2 (amino acids 1-174; SEQ ID NO: 2) fused to the N-terminus of a human IgG1 Fc region through a Gly-Ser-Ser linker. Animals were immunized with the soluble TREM2 protein mixed with CpG oligodeoxynucleotides (CpG-ODN) or CpG-ODN and polyinosinic:polycytidylic acid (Poly I:C) and QS-21 adjuvant, 8-12 times over 4-8 weeks using subcutaneous injections. The initial boost contained 10 µg of protein while subsequent boosts contained 5 µg of protein.

[0260] The immunogen for genetic immunization was created by coating gold beads (BioRad, Hercules, California) with mouse GM-CSF, CpG-ODN, and expression vectors encoding wild-type human TREM2 (SEQ ID NO: 1) and wild-type human DAP12 (SEQ ID NO: 3). The genetic immunogen was delivered to the epidermis of a shaved mouse abdomen using the Helios Gene Gun system according to the manufacturer's instructions (BioRad, Hercules, California). Mice were immunized with the genetic immunogen 12-16 times over 6-8 weeks.

[0261] Human TREM2-specific serum titers were monitored by live-cell FACS analysis on an Accuri or FACS Calibur (BD Biosciences) flow cytometer or by TREM2-specific ELISA. Animals with the highest serum native titers directed against human TREM2 from four separate harvests were sacrificed and used for hybridoma generation. Table 7 below provides a description of each harvest group.

Table 7. TREM2 Immunization Groups

Group	Immunogen	Adjuvant	XenoMouse® Strain	Harvest
Harvest 1	Human TREM2 soluble protein	CpG	G2K	3 mice
			G2KL	3 mice
Harvest 3	Human TREM2 soluble protein	CpG + Poly I:C + QS-21	G2K	6 mice
			G2KL	4 mice
Harvest 4	pTT5 vector/human TREM2 + pTT5 vector/human DAP12	CpG + mGM-CSF	G2K	10 mice
			G2KL	4 mice
Harvest 5	pTT5 vector/human TREM2 + pTT5 vector/human DAP12	CpG + mGM-CSF	G4K	4 mice
			G4KL	4 mice

Preparation of Monoclonal Antibodies

[0262] Animals exhibiting suitable antigen-specific serum titers were identified and lymphocytes were obtained from spleen and/or draining lymph nodes. Pooled lymphocytes (from each harvest) were dissociated from lymphoid tissue by grinding in a suitable medium (for example, Dulbecco's Modified Eagle Medium (DMEM); Invitrogen, Carlsbad, CA). B cells were selected and/or expanded using standard methods, and fused with a suitable fusion partner (e.g. non-secretory myeloma P3X63Ag8.653 cells) using conventional techniques.

[0263] For harvest 1, fused hybridoma pools from select immune tissue harvest were plated as polyclonal wells, exhausted to generate conditioned media, and then screened for binding to the soluble human TREM2 protein (fusion protein described above). The hits from this plating were pooled and then clonally FACS-sorted to obtain one live cell per well. For harvest 3, 4 and 5, fused hybridoma pools from select immune tissue were used as a source of material for FACS-based enrichments. Specifically, hybridoma cells were thawed and cultured in DMEM selection media for 3-4 days. Media was changed to BDQY hybridoma media a day before bulk sort. Cells were washed in 10 mL sterile FACS buffer and then incubated with biotinylated soluble TREM2 protein at 2 to 5 µg/mL concentration at 1 mL reaction volume for 1 hour at 4° C. For the harvest 3 group, which was immunized with soluble TREM2 protein, this step was performed in the presence of 100 µg/mL polyclonal human IgG (Jackson ImmunoResearch) to block any binders to the Fc region. The polyclonal human IgG blocking step was omitted for harvest 4 and 5 as these harvests were from genetically-immunized animals.

[0264] After one dilution wash in 10 mL FACS buffer, 1 mL antibody cocktail containing 5 µg/mL each of Alexa Fluor 488 conjugated goat anti-human IgG (Jackson Immunoresearch) and Alexa Fluor 647 conjugated streptavidin (Jackson Immunoresearch) was added to the cells. The cells were then incubated at 4° C for 30 minutes. After the incubation, the cells were washed in 10 mL FACS buffer, resuspended in 2 mL of BDQY hybridoma media containing 5 µL of 7-AAD (BD Pharmingen, Cat: 559925), then put through a 40 micron cell strainer to remove any clumps. Cells were bulk sorted on BD FACSAria by gating on live cell population dual positive for Alexa Fluor 488 and Alexa Fluor 647 fluorescence signals.

[0265] Sorted cells were transferred into 24-well tissue culture plates and cultured for a few days before they were counted and stained again using the method described above to check for enrichment of antigen specific cells. The cells were then single cell sorted into 384-well microtiter plates containing BDQY hybridoma media and cultured for up to 2 weeks before the supernatants were collected for screening.

Example 2. Selection of TREM2-Specific Binding Antibodies

[0266] Antibodies produced from the hybridomas described in Example 1 were screened for binding to human TREM2, agonist activity of human TREM2, and cross-reactivity to other TREM proteins. The methods and results of these screens are described below.

Primary TREM2 Binding Screen

[0267] Exhausted hybridoma supernatants were tested for binding to human TREM2 by ELISA. Briefly, neutravidin plates were generated by incubating a 384 well Corning Assay Plate 3702 with neutravidin (Thermo 3100B) at 10 µg/mL (40 µL/well) in 1X PBS at 4°C overnight. The plates were washed with 1X PBS using a Biotek plate washer and then blocked with 1% milk/1X PBS (90 µL/well) at room temperature (RT) for 30 minutes. The plates were then washed again with 1X PBS using the plate washer. The capture sample was biotinylated soluble human TREM2 protein (TREM2 ECD-huIgG1 Fc fusion protein) and was added at 0.5 µg/mL in 1% milk/1X PBS at a volume of 40µL/well. The plates were then incubated at RT for 1 hour to immobilize the TREM2 protein to the wells of the plates. Following the incubation, the plates were again washed with 1X PBS using the plate washer. 10µL of each hybridoma supernatant to be tested and 40µL of 1% milk/1X PBS (1:5 dilution) were added to each well of the plates and incubated at RT for 1 hour. Again, the plates were washed with 1X PBS using the plate washer. Goat anti-human kappa-HRP (Southern Biotech, 2060-05) and goat anti-human lambda-HRP (Southern Biotech, 2070-05) diluted together 1:2000 in 1% milk/1X PBS or goat anti-human IgG Fc POD diluted 1:4000 in 1% milk/1X PBS was added to the plates (40 µL/well) and the plates were incubated at RT for 1 hour. After the plates were washed with 1X PBS using the plate washer, 40 µL/well of TMB substrate (Neogen, lot # 150114) was added to the plates and the plates were incubated at RT for 30 minutes. The reaction was quenched with 1N hydrochloric acid (40uL/well) following the incubation period. OD readings at 450 nm were obtained with a plate reader.

[0268] The primary ELISA screen identified 2,523 antibodies that were positive for TREM2 binding from the four separate harvests groups. These identified antibodies were advanced to the functional assay screens.

TREM2 Functional Assay Screens

[0269] The antibodies that tested positive for TREM2 binding in the ELISA assay were evaluated for agonist activity of human TREM2 in a cell-based phospho-Syk (pSyk) signaling assay. Human TREM2, which is a transmembrane glycoprotein, couples with the adaptor protein, DAP12, for signaling and function through the recruitment of tyrosine kinases ζ -chain associate protein 70 (ZAP70) and spleen tyrosine kinase (Syk)(Colonna, Nature Reviews Immunology, Vol. 3: 445-453, 2003). The phosphorylated form of Syk is indicative of activation of TREM2/DAP12 signaling. Thus, a cell-based AlphaLISA (Perkins Elmer) assay to detect phosphorylated forms of Syk in response to TREM2/DAP12 modulation was developed. The assay employs a rabbit-anti-pSyk antibody, a biotinylated mouse anti-total Syk antibody, acceptor beads conjugated to anti-rabbit IgG antibodies, and donor beads coated with streptavidin. Phosphorylated forms of Syk present in cell lysates are bound by both the rabbit-anti-pSyk antibody and the mouse anti-total Syk antibody. The acceptor beads, which are conjugated to an anti-rabbit IgG antibody, bind to the rabbit anti-pSyk antibody, and the streptavidin-coated donor beads bind to the biotinylated mouse anti-total Syk antibody. Excitation of the donor beads at a wavelength of 680 nm results in the release of singlet oxygen, which in turn produces an amplified fluorescent signal in the acceptor beads, thereby producing an emission at 615 nm. The emission at 615 nm is not detected if the donor and acceptor beads are not located within close proximity to each other (i.e. acceptor bead is not recruited to the complex because Syk is not phosphorylated and thus, not bound by the rabbit anti-pSyk antibody). Thus, the amount of light emitted at 615 nm is proportional to the amount of phosphorylated Syk present in the cell lysate, which in turn is indicative of activation of TREM2/DAP12 signaling by the anti-TREM2 antibody.

[0270] HEK293T cells stably expressing human TREM2 and human DAP12 (G13 cell line) were plated in growth media at 40,000 cells per well (in 90 or 80 μ L) in tissue culture treated 96-half area well plates or 50,000 cells per well (in 200 μ L) in poly-D-lysine-coated plates. The cells were incubated overnight at 37°C and 5% CO₂. Anti-human TREM2 antibodies were added either at a single concentration (for initial single point screening) or a range of concentrations (for potency testing). After incubation of cells and antibody at room temperature for 30 to 40 minutes, culture media was completely removed. The cells were lysed with 20 μ L (for 40,000 cells) or 25 μ L (for 50,000 cells) of lysis buffer containing protease/phosphatases inhibitors on ice for 45 to 60 minutes. The cell lysate (5 μ L) was transferred to appropriate wells of a 384-well white assay plate containing a 15 μ L mixture of rabbit anti-pSyk antibody (final concentration: 1 nM), biotinylated mouse anti-Syk antibodies

(final concentration: 1 nM) and acceptor beads conjugated to anti-rabbit IgG antibodies (final concentration: 10 µg/mL). The assay plates were then incubated on ice for 2 hours. Donor beads coated with streptavidin (5 µL) were subsequently added to the wells (final concentration: 40 µg/mL) and the assay plates were incubated at room temperature for 1 hour in the dark. The AlphaLISA signal (counts) was measured by EnVision Multilabel Reader. The antibody agonist activity was reported as fold over control (S/B): S/B= Sample pSyk signal (counts)/Basal pSyk signal (isotype control pSyk signal counts).

[0271] Antibodies from the hybridoma supernatants that tested positive for TREM2 binding were initially tested at a single concentration in the pSyk assay. For this single point screening, exhausted hybridoma supernatant (ESN) containing anti-huTREM2 antibody was added to the cells either based on volume (10 µL for harvest 1, 1:10 dilution) or concentration (20 µL of ESN that was previously normalized to 10 µg/mL for harvest 3, 4 and 5, 1:5 dilution). Of the 2,523 antibodies positive for TREM2 binding from the four separate harvests, 140 antibodies exhibited activity in the pSyk assay at a single concentration. These antibodies were advanced for potency screening.

[0272] Potency screening was initially performed on unpurified, quantitated clonal hybridoma-derived anti-TREM2 antibodies and later on purified hybridoma-derived and/or recombinant monoclonal antibodies. For harvest 1, the anti-TREM2 antibodies were serially titrated at 3-fold from 100 µg/mL to 0.005 µg/mL and 10 µL of each dilution was added to the cells (final antibody concentrations from 10 µg/mL to 0.0005 µg/mL, 66.67 nM to 0.003 nM). For potency screening of harvest 3, 4, and 5, the culture medium was completely removed from the cells. The anti-TREM2 antibodies were serially titrated at 3 fold from 2 µg/mL to 0.003 µg/mL in growth media and 50 µL of each dilution was added to the cells (final antibody concentration from 13.33 nM to 0.02 nM). The EC₅₀ values for each anti-TREM2 antibody was determined by a four-parameter logistic fit model of GraphPad Prism Version 6.07 from the 10-point dose response curves.

[0273] Of the 140 antibodies screened for potency, 93 antibodies were selected for further screening and characterization. Figure 1A shows the dose-response curves for the top agonist anti-TREM2 antibodies from harvest 1, whereas Figure 1B shows the dose-response curves for the top agonist anti-TREM2 antibodies from harvests 3, 4, and 5. EC₅₀ values for the top 18 antibodies from all four harvests are provided in Table 8 below. As evident from the low nanomolar or subnanomolar EC₅₀ values, the majority of the anti-TREM2 antibodies are potent agonists of TREM2/DAP12 signaling. Several of the antibodies are more potent and

produce a greater level of maximum activation of TREM2/DAP12 signaling than a commercially available rat anti-human/mouse TREM2 antibody (mAb17291; Rat IgG2b Clone #237920, R&D Systems), which had an EC50 value of 0.50 nM and an Emax of 13.8 in this assay. Importantly, the agonist activity of the anti-TREM2 antibodies was observed in the absence of a cross-linking agent (e.g. protein G, protein A, or anti-human secondary antibody) or immobilization of the antibodies (e.g. plate-bound antibodies), suggesting the antibodies can effectively engage and activate human TREM2 in a soluble, monomeric form. For many agonist antibodies, cross-linking of their Fc regions is required to cluster the antibodies to activate effectively the target receptor. *See, e.g.*, Natoni *et al.*, British Journal of Haematology, Vol. 139: 568–577, 2007; Vonderheide and Glennie, Clin. Cancer Res., Vol. 19: 1035-1043, 2013. Such a cross-linking requirement to achieve agonist activity for other TREM2 antibodies has been observed. *See, e.g.*, U.S. Patent No. 8,981,061 and WO 2016/023019. The TREM2 antibodies described herein have an advantage over these other TREM2 antibodies in that they are cross-linking independent agonists of human TREM2 (e.g. they do not require cross-linking or oligomerization via their Fc domains for agonistic activity).

Selectivity and Cross-Reactivity of TREM2 Antibodies

[0274] The anti-TREM2 antibodies demonstrating agonist activity in the potency screen were further evaluated for cross-reactivity to mouse and cynomolgus TREM2 as well as cross-reactivity to human TREM1 protein. For the species cross-reactivity screen, HEK293 cells were transfected with expression vectors comprising either mouse TREM2 and mouse DAP12 cDNA or cynomolgus TREM2 and cynomolgus DAP12 cDNA, Gibco™ Opti-MEM® media (Gibco, Cat. No. 31985088) and 293Fectin™ reagent (Invitrogen, Cat. No. 12347019) following the protocol set out by the manufacturer. TREM1 cross-reactivity was assessed using a cell line stably expressing human TREM1/DAP12. Hybridoma supernatants were screened for the presence of monoclonal antibodies binding to human TREM1, mouse TREM2 or cynomolgus TREM2 by incubating the supernatants on each of the transfected cells for 1 hour, followed by wash steps. The cells were then incubated with a goat anti-human Fc antibody conjugated to Alexa Fluor 647 (Jackson Immunochemicals 109-605-098) for 15 minutes. The binding was detected by FACS using the Accuri FACS machine with Intellicyt autosampler. Irrelevant isotype control antibodies were included in the FACS analysis. The data was reported as geomean (GM) fold over irrelevant control antibody

binding. Of the 93 antibodies from the four harvests screened for cross-reactivity, 50 antibodies were cross-reactive with cynomolgus TREM2 and 9 antibodies were cross-reactive with mouse TREM2. None of the tested antibodies were cross-reactive with human TREM1. The data from all screens for the top 18 anti-TREM2 monoclonal antibodies from all four harvests are summarized in Table 8 below.

Table 8. Summary Data for Top Anti-TREM2 Monoclonal Antibodies from Hybridoma Screen

Antibody ID	OD 450 human TREM2 (ELISA)	Isotype	pSyk fold over control	pSyk EC50 (nM)	Cyno TREM2 GM Fold	Mouse TREM2 GM Fold	Human TREM1 GM Fold
4C5	3.62	G2	9.26	0.18	42.3	0.4	0.8
4G10	3.17	G2	11.72	0.47	96.3	4.1	1.2
5E3	3.88	G2	8.02	0.24	89.6	2.6	1.1
6E7	3.17	G2	13.69	0.29	82.7	1.2	1.2
24A10	2.75	G2	6.8	32.9	1.4	1.1	1.1
24F4	1.20	G2	5.8	2.4	34.0	10.1	1.2
24G6	2.76	G2	11.8	1.0	12.2	0.9	1.3
25F12	1.29	G2	4.2	2.6	2.2	0.8	1.2
26A10	1.16	G2	6.0	1.3	37.5	0.8	1.5
26C10	1.59	G2	4.8	2.2	46.0	0.9	1.7
26F2	1.48	G2	5.4	1.4	72.8	1.1	1.6
32E3	1.41	G2	8.2	1.2	31.0	1.0	1.1
33B12	1.34	G2	6.0	1.0	21.7	1.0	1.4
10E3	0.55	G2	12.1	0.4	82.8	1.1	1.6
12G10	3.49	G2	11.1	0.4	2.1	1.1	1.1
13E7	0.73	G2	11.4	0.4	67.5	1.1	1.4
14C12	0.71	G2	11.1	0.4	63.2	1.1	1.4
16B8	0.59	G4	ND	ND	23.3	1.1	1.1

Example 3. Sequencing of Human Anti-TREM2 Agonist Antibodies

[0275] RNA (total or mRNA) was purified from wells containing the TREM2 agonist antibody-producing hybridoma cells using a Qiagen RNeasy mini or the Invitrogen mRNA catcher plus kit. Purified RNA was used to amplify the antibody heavy and light chain variable region (V) genes using cDNA synthesis via reverse transcription, followed by a polymerase chain reaction (RT-PCR). The fully human antibody gamma heavy chain was obtained using the Qiagen One Step Reverse Transcriptase PCR kit (Qiagen). This kit was used to generate the first strand cDNA from the RNA template and then to amplify the variable region of the gamma heavy chain using multiplex PCR. The 5' gamma chain-specific primer annealed to the signal sequence of the antibody heavy chain, while the 3' primer annealed to a region of the gamma constant domain. The fully human kappa light chain was obtained using the Qiagen One Step Reverse Transcriptase PCR kit (Qiagen). This kit was used to generate the first strand cDNA from the RNA template and then to amplify the variable region of the kappa light chain using multiplex PCR. The 5' kappa light chain-specific primer annealed to the signal sequence of the antibody light chain while the 3' primer annealed to a region of the kappa constant domain. The fully human lambda light chain was obtained using the Qiagen One Step Reverse Transcriptase PCR kit (Qiagen). This kit was used to generate the first strand cDNA from the RNA template and then to amplify the variable region of the lambda light chain using multiplex PCR. The 5' lambda light chain-specific primer annealed to the signal sequence of light chain while the 3' primer annealed to a region of the lambda constant domain.

[0276] The amplified cDNA was purified enzymatically using exonuclease I and alkaline phosphatase and the purified PCR product was sequenced directly. Amino acid sequences were deduced from the corresponding nucleic acid sequences bioinformatically. Two additional, independent RT-PCR amplification and sequencing cycles were completed for each hybridoma sample in order to confirm that any mutations observed were not a consequence of the PCR. Amino acid sequences for the light chain variable regions and associated CDRs for exemplary antibodies are provided in Table 1A, whereas amino acid sequences for the heavy chain variable regions and associated CDRs for the antibodies are provided in Table 1B. Table 6 provides nucleic acid sequences encoding the light and heavy chain variable regions of the exemplary antibodies.

[0277] The derived amino acid sequences for each light and heavy chain variable region were then analyzed to determine the germline sequence origin of the antibodies and to identify deviations from the germline sequence. A comparison of each of the light chain and heavy chain variable region sequences to their original germline sequences are shown in Figures 2A-4B. The identity of the germline genes is indicated next to each antibody clone number. The amino acid sequences corresponding to CDRs of the sequenced antibodies were aligned and these alignments were used to group the clones by similarity.

Example 4. Epitope Binning Analysis of Agonist Anti-TREM2 Antibodies

[0278] Epitope bins of a subset of agonist anti-human TREM2 antibodies were determined using anti-human Fc (Kinetic) sensors (18-5090) on an Octet® HTX instrument (Pall ForteBio). Each of sixteen different anti-TREM2 antibodies produced from hybridomas were quantitated and loaded onto one of the anti-human Fc sensors at 5 µg/mL for 2 minutes ("Load Antibody"). The sensor was then blocked with 100 µg/mL of an irrelevant human IgG2 antibody for 5 minutes. A recombinant soluble human TREM2 protein (human TREM2 extracellular domain (amino acids 1-174) coupled to a Flag/His tag (human TREM2 ECD-FlagHis)) was added to the sensor at 4 µg/mL for 5 minutes to allow binding of the soluble TREM2 protein to the load antibody. Next, each of the sixteen different anti-TREM2 antibodies ("Sandwich Antibody") was added to the sensor at 5 µg/mL and allowed to bind for 5 minutes. All assay buffers contained 10 mM Tris (pH 7.6), 0.1 % Triton X-100, 150 mM NaCl, 1 mM CaCl₂, and 1 mg/mL BSA. The assay was conducted at 25° C. Experimental kinetic results were fit to a 1:1 binding model.

[0279] If the load antibody and the sandwich antibody bind to a similar epitope on human TREM2, then the addition of the sandwich antibody to the sensor will not produce a binding event. However, if addition of the sandwich antibody produces a binding event, then the sandwich antibody binds to a different epitope on human TREM2 than the load antibody and the two antibodies are categorized into different epitope bins. Figure 5 depicts binding data from a sensor loaded with the 6E7 antibody and exposed to either the 5E3 antibody or the 6E7 antibody as the sandwich antibody. As expected, an increase in binding was observed with the addition of the soluble human TREM2 protein indicating that the 6E7 antibody specifically bound an epitope on human TREM2. No further binding was observed when 6E7 was added as the sandwich antibody as the sensor-immobilized 6E7 antibody was already bound to this particular epitope on human TREM2. However, when the 5E3 antibody was

added as the sandwich antibody, an increase in binding was observed, indicating that the 5E3 antibody binds to a different epitope on human TREM2 than the 6E7 antibody.

[0280] A summary of the epitope binning data for sixteen different anti-TREM2 antibodies is shown below in Table 9. Based on the binding data, the antibodies could be grouped into four distinct epitope bins. Antibodies 10E3, 13E7, 24F4, 4C5, 4G10, 32E3, and 6E7 appear to share a similar epitope (bin A), which is different than the epitope bound by antibodies 16B8, 26A10, 26C10, 26F2, 33B12, and 5E3 (bin B). Antibodies 24A10 and 24G6 share a similar epitope on human TREM2 (bin C), whereas antibody 25F12 has a distinct binding epitope (bin D) from any of the other tested antibodies.

Table 9. Summary of Epitope Binning Analysis

	Sandwich Antibody																Bin
Load Ab	10E3	13E7	24F4	4C5	4G10	32E3	6E7	16B8	26A10	26C10	26F2	33B12	5E3	24A10	24G6	25F12	
10E3	-0.024	-0.019	-0.032	-0.005	-0.019	-0.023	0.051	0.280	0.259	0.285	0.275	0.271	0.222	0.347	0.331	0.889	A
13E7	-0.019	-0.017	-0.015	ND	ND	-0.027	0.051	0.312	0.272	0.323	0.294	0.287	0.259	0.375	0.356	0.104	A
24F4	-0.002	-0.002	0.038	ND	ND	-0.021	0.054	0.454	0.449	0.552	0.477	0.454	0.434	0.585	0.523	0.180	A
4C5	0.000	ND	ND	-0.014	-0.018	-0.016	ND	ND	ND	0.368	ND	ND	ND	ND	0.438	0.154	A
4G10	-0.008	ND	ND	-0.011	-0.026	-0.020	ND	ND	ND	ND	0.334	ND	ND	ND	0.376	0.142	A
32E3	0.007	0.010	-0.001	-0.010	-0.029	-0.010	0.079	0.400	0.362	0.419	0.411	0.384	0.336	0.461	0.444	0.236	A
6E7	-0.012	-0.010	-0.039	ND	ND	-0.024	0.008	0.504	0.491	0.594	0.523	0.520	0.514	0.516	0.583	0.213	A
16B8	0.330	0.329	0.270	ND	ND	0.120	0.429	-0.009	-0.018	-0.031	-0.003	-0.017	-0.047	0.481	0.481	0.252	B
26A10	0.367	0.371	0.319	ND	ND	0.157	0.475	0.028	-0.001	-0.017	0.009	0.023	-0.052	0.596	0.557	0.347	B
26C10	0.348	0.369	0.346	ND	ND	0.141	0.472	0.006	-0.033	-0.032	-0.003	-0.009	-0.073	0.605	0.554	0.327	B
26F2	0.354	0.363	0.282	0.31	0.18	0.143	0.506	0.031	-0.016	-0.015	-0.008	0.002	-0.045	0.544	0.529	0.330	B
33B12	0.303	0.303	0.250	ND	ND	0.132	0.434	0.007	-0.020	-0.033	-0.009	-0.014	-0.055	0.439	0.446	0.275	B
5E3	0.415	0.428	0.311	ND	ND	0.176	0.565	-0.004	-0.027	-0.042	-0.014	-0.015	-0.165	0.530	0.552	0.335	B
24A10	0.380	0.383	0.335	ND	ND	0.162	0.495	0.423	0.454	0.541	0.490	0.470	0.441	0.023	0.000	0.340	C
24G6	0.317	0.338	0.251	0.268	0.184	0.126	0.412	0.365	0.354	0.384	0.399	0.388	0.328	-0.031	-0.019	0.284	C
25F12	0.273	0.278	0.244	0.265	0.199	0.154	0.371	0.399	0.343	0.418	0.366	0.345	0.380	0.509	0.488	0.011	D

Example 5. Binding Affinity Determination of Agonist Anti-TREM2 Antibodies

[0281] To quantitate the binding affinity of agonist antibodies for human TREM2, association and dissociation rate constants as well as the equilibrium dissociation constant were determined using anti-human Fc (Kinetic) sensors on an Octet® HTX instrument (Pall ForteBio). Agonist anti-TREM2 antibodies were made up in DMEM null media, 250 μ L at 10 μ g/mL. The, 250uL of assay buffer (10 mM Tris (pH 7.6), 0.1% Triton X-100, 150 mM NaCl, 1mM CaCl₂, and 1 mg/mL BSA) was added to the antibody solutions to a final volume of 500 μ L and final antibody concentration of 5 μ g/mL. The anti-human Fc sensor was pre-incubated in 200 μ L of the assay buffer for a minimum of 10 minutes. The sensor was then regenerated for 5 seconds in 10 mM glycine pH 1.5. Test agonist anti-TREM2 antibodies were loaded onto the sensor for 2 minutes, and baseline measurements were taken for 2 minutes. The antibody-loaded sensor was bound to recombinant soluble human TREM2

protein (human TREM2 extracellular domain (amino acids 1-174) coupled to a Flag/His tag (human TREM2 ECD-FlagHis)) or recombinant soluble cynomolgus TREM2 protein (cynomolgus TREM2 extracellular domain coupled to a Flag/His tag) in a 2-fold serial dilution series starting at 100 nM with a 6-point dilution series. The recombinant TREM2 proteins were allowed to associate with the antibody-loaded sensor for 10 minutes, and then dissociation was measured for 10 minutes. The assay was conducted at 25° C. Experimental kinetic results were globally fit to a 1:1 binding model in order to determine the association and dissociation rate constants as well as the equilibrium dissociation constant. Table 10 provides the results of the assay for human TREM2 for select antibodies and Table 11 provides the results of the assay for cynomolgus TREM2 for select antibodies.

Table 10. Binding Affinity for Human TREM2

Antibody ID	K _D (M)	k _a (M ⁻¹ s ⁻¹)	k _d (s ⁻¹)
4C5	3.1E-09	1.6E+05	4.9E-04
4G10	3.3E-09	3.0E+05	9.8E-04
5E3	2.1E-09	2.5E+05	5.3E-04
6E7	2.6E-09	2.7E+05	6.9E-04
10E3	1.03E-08	1.77E+05	1.82E-03
13E7	1.10E-08	1.44E+05	1.58E-03
24G6	3.13E-09	2.20E+05	6.88E-04

Table 11. Binding Affinity for Cyno TREM2

Antibody ID	K _D (M)	k _a (M ⁻¹ s ⁻¹)	k _d (s ⁻¹)
4C5	3.6E-09	3.3E+05	1.2E-03
4G10	1.7E-09	5.6E+05	9.6E-04
5E3	1.6E-09	7.0E+05	1.1E-03
6E7	2.5E-09	4.6E+05	1.1E-03
10E3	1.13E-08	3.24E+05	3.66E-03
13E7	8.71E-09	2.72E+05	2.37E-03

Antibody ID	K _D (M)	k _a (M ⁻¹ s ⁻¹)	k _d (s ⁻¹)
24G6	1.99E-08	4.86E+05	9.65E-03

Example 6. Agonist Activity of Anti-TREM2 Antibodies in THP-1 Cells

[0282] Select anti-TREM2 antibodies were evaluated for their ability to activate human TREM2/DAP12 signaling in THP-1 cells. The THP-1 cell line is a human leukemia monocytic cell line, which is commonly used as an *in vitro* model of human monocyte and macrophage function (Chanput *et al.*, International Immunopharmacology, Vol. 23: 37-45, 2014).

[0283] Suspension THP-1 cells (1×10^6 cells/mL) were differentiated by incubation in growth media (RPMI, 10% FBS (heat inactivated, 1% Glutamax, 1% Hepes, 1% Pen/Strep) containing 20 nM Phorbol 12-myristate 13-acetate (PMA) at 37°C /5% CO₂ for 72 hours. After 72 hours stimulation, the cells attached to the surface of tissue culture-treated dishes. PMA was gently washed off with PBS, and replenished in fresh growth media containing 10 ng/mL IL-4. The cells were continually incubated at 37°C /5% CO₂ for another 72 hours. On day 6 (end of cell differentiation), the cells were harvested with non-enzymatic cell dissociation buffer or cell stripper and were plated in growth media at 100,000 cells per well into tissue culture-treated 96 - well plates. The cells were incubated overnight at 37°C /5% CO₂.

[0284] On the following day, the cells were treated with anti-human TREM2 antibodies for 10 minutes at room temperature, and the media was subsequently removed. The cells were lysed with 30 μ L lysis buffer for 45 to 60 minutes on ice. The cell lysate (5 μ L) was transferred into 384 well plates for determination of phosphorylated Syk (pSyk) levels using the AlphaLISA assay described in Example 2. The EC₅₀ for each anti-TREM2 antibody was determined from a dose-response curve by a four-parameter logistic fit model of GraphPad Prism Version 6.07.

[0285] The results of the experiment are shown in Figure 6 and Table 12. All of the tested anti-TREM2 antibodies induced pSyk levels in a dose-dependent manner in the differentiated THP-1 cells. All of the anti-TREM2 antibodies produced greater activation of Syk than mAB17291 ("RnD"), a commercial rat anti-human/mouse antibody (Rat IgG2b Clone #237920, R&D Systems), with ten of the antibodies producing a 2-fold or greater maximum activation than the commercial antibody. Antibodies 10E3 and 13E7 exhibited the highest Emax values, which were about 4.5-fold greater than that that for the commercial antibody.

Table 12. Activation of TREM2/DAP12 Signaling in THP-1 Cells by Anti-TREM2

Antibodies

Antibody ID	EC50 (nM)	E _{max} *
4C5	1.715	265.4
4G10	0.5791	235.7
5E3	0.5935	194.8
6E7	0.8989	273.4
10E3	1.004	456.5
13E7	0.4617	459.6
16B8	0.4176	139.8
24G6	0.6622	221.1
25F12	1.048	121.5
26F2	0.07778	207.4
32E3	1.246	196.6
33B12	2.845	245.7
RnD	0.3834	100*

*E_{max} = % maximum activation of antibody compared to RnD antibody (fixed as 100%)**Example 7. Engineering of Agonist Anti-TREM2 Antibodies**

[0286] A subset of the anti-TREM2 antibodies were selected for subsequent engineering to improve the biophysical, expression, and/or stability properties of the antibodies. Light and heavy chain variable region sequences of antibodies 10E3, 13E7, 4C5, 6E7, 5E3, and 24G6 were analyzed for potential chemical hotspots (e.g. aspartate isomerization, asparagine deamidation, and tryptophan oxidation) and covariance violations. Correction of covariance violations can improve thermal stability, expression, and biophysical properties of antibodies (see, e.g., WO 2012/125495). Tables 13-18 below summarize the results of the sequence analysis for each of the six antibodies and identify specific mutations at particular positions within the heavy and light chain variable region sequences that can be made to improve the stability, expression, and/or biophysical properties of the antibodies. The particular region (e.g. framework regions 1, 2, 3, or 4 (FR1, FR2, FR3, or FR4) or complementarity determining regions 1, 2, or 3 (CDR1, CDR2, or CDR3) within the sequence are also indicated.

Table 13. Engineered Variants of 10E3 Antibody

Position in 10E3 VL Sequence or VH sequence	Region	Hot Spot	Parent Amino Acid	Amino Acid Substitutions
<i>Light chain variable sequence (SEQ ID NO: 54)</i>				
64	FR3	Covariance violator	V	G, A
79	FR3	Covariance violator	Q	E, D
80	FR3	Covariance violator	S	P, A
85	FR3	Covariance violator	F	V, L, A, D, I, L, M, T
94	CDR3	Potential Tryptophan Oxidation Site	W	F, Y, S, T, A, H, I, Q
100	FR4	Covariance violator	P	R, Q, G
<i>Heavy chain variable sequence (SEQ ID NO: 117)</i>				
19	FR1	Covariance violator	M	K, R, T, E, N, Q
55-56	CDR2	Potential Isomerization Site	DS	ES, QS, DA, NS, DQ, TS, DV
57-58	CDR2	Potential Isomerization Site	DT	ST, ET, DA, DV, QT
104	CDR3	Potential Tryptophan Oxidation Site	W	F, Y, T, S, A, H, I, Q

Table 14. Engineered Variants of 13E7 Antibody

Position in 13E7 VL Sequence or VH sequence	Region	Hot Spot	Parent Amino Acid	Amino Acid Substitutions
<i>Light chain variable sequence (SEQ ID NO: 55)</i>				
64	FR3	Covariance violator	V	G, A
79	FR3	Covariance violator	Q	E, D
80	FR3	Covariance violator	S	P, A
94	CDR3	Potential Tryptophan Oxidation Site	W	F, Y, S, T, A, H, I, Q
100	FR4	Covariance violator	P	R, Q, G
<i>Heavy chain variable sequence (SEQ ID NO: 118)</i>				
19	FR1	Covariance violator	M	K, R, T, E, N, Q
55-56	CDR2	Potential Isomerization Site	DS	ES, QS, DA, DQ, NS, TS, DV

Position in 13E7 VL Sequence or VH sequence	Region	Hot Spot	Parent Amino Acid	Amino Acid Substitutions
57-58	CDR2	Potential Isomerization Site	DT	ST, ET, DA, DV, QT
104	CDR3	Potential Tryptophan Oxidation Site	W	F, Y, T, S, A, H, I, Q

Table 15. Engineered Variants of 4C5 Antibody

Position in 4C5 VL Sequence or VH sequence	Region	Hot Spot	Parent Amino Acid	Amino Acid Substitutions
<i>Light chain variable sequence (SEQ ID NO: 60)</i>				
60	FR3	Covariance violator	L	S, P, D, A
92-93	CDR3	Potential Isomerization Site	DS	ES, QS, DA, DN, DQ, TS, NS, DV
<i>Heavy chain variable sequence (SEQ ID NO: 123)</i>				
27	FR1	Covariance violator	H	Y, D, F, N
55-56	CDR2	Potential Isomerization Site	DS	ES, QS, DA, DQ, DV, TS, NS
57-58	CDR2	Potential Isomerization Site	DT	ST, ET, DA, DV, QT
105-106	CDR3	Potential Isomerization Site	DS	ES, QS, DA, DQ, DV, TS, NS, GT

Table 16. Engineered Variants of 6E7 Antibody

Position in 6E7 VL Sequence or VH sequence	Region	Hot Spot	Parent Amino Acid	Amino Acid Substitutions
<i>Light chain variable sequence (SEQ ID NO: 61)</i>				
56-57	CDR2/FR3 boundary	Potential Deamidation Site	NG	SG, TG, QG, NA, EG, NV
92-93	CDR3	Potential Isomerization Site	DS	ES, QS, DA, DN, DQ, DV, TS, NS
<i>Heavy chain variable sequence (SEQ ID NO: 124)</i>				
55-56	CDR2	Potential Isomerization Site	DS	ES, QS, DA, DQ, DV, TS, NS
57-58	CDR2	Potential Isomerization Site	DT	ST, ET, DA, DV, QT
105-106	CDR3	Potential Isomerization Site	DS	ES, QS, DA, DQ, DV, TS, NS, GT

Table 17. Engineered Variants of 5E3 Antibody

Position in 5E3 VL Sequence or VH sequence	Region	Hot Spot	Parent Amino Acid	Amino Acid Substitutions
<i>Light chain variable sequence (SEQ ID NO: 62)</i>				
36	FR2	Consensus violator	F	Y
46	FR2	Covariance violator	S	L, R, V, F
61	FR3	Consensus violator	K	R
100	FR4	Covariance violator	P	Q, G, R
<i>Heavy chain variable sequence (SEQ ID NO: 125)</i>				
43	FR2	Covariance violator	L	Q, K, H
76	FR3	Covariance violator	I	T
85	FR3	Covariance violator	R	S, G, N, D
99-100	CDR3	Potential Isomerization Site	DG	EG, DA, DY, DV, QG, SG, TG
116	FR4	Covariance violator	T	L, M, P, R

Table 18. Engineered Variants of 24G6 Antibody

Position in 24G6 VL Sequence or VH sequence	Region	Hot Spot	Parent Amino Acid	Amino Acid Substitutions
<i>Light chain variable sequence (SEQ ID NO: 52)</i>				
91	FR3	Covariance violator	F	V, I, T, L, D
<i>Heavy chain variable sequence (SEQ ID NO: 115)</i>				
62-63	CDR2	Potential Isomerization Site	DS	ES, QS, DA, DQ, TS, DV, NS

Table 19. Exemplary Variable Region Amino Acid Sequences of Engineered Antibodies

Ab ID.	LC variable region sequence	HC variable region sequence
24G6	DIVMTQSPDSLAVSLGERATINCKSS	EVQLLES GGGLVQPGGSLRLSC
(SST28	QSVLYSSNNKHFLAWYQQKPGQPP	AASGFTFSSYAMSWVRQAPGK
347 and	KLLIWASTRESGVPDRFSGSGSGT	GLEWVSAISGSGGSTYYAESVK
SST20	DFTLTISLQAEDVAVYYCQQYYST	GRFTISRDN SKNTLYLQMNSLR
4812)	PLTFGGGTKVEIK (SEQ ID NO: 326)	AEDTAVYYCAKAYTPMAFFDY

		WGQGTLLVTVSS (SEQ ID NO: 327)
6E7 (SST29 857)	DIQMTQSPSSVSASVGDRVITICRAS QGISSWLAWYQQKPGKAPKLLIYAA SSLQSGVPSRFSGSGSGTDFTLTISL QPEDFATYFCQQADAFPRTFGQGTK LEIK (SEQ ID NO: 328)	EVQLVQSGAEVKKPGESLKISC KSGYSFTSYWIAWVRQMPGK GLEWMGIIYPGDADARYSPSFQ GQVTISADKSISTAYLQWSSLKA SDTAMYFCARQRTFYDSSDYF DYWGQGTLLVTVSS (SEQ ID NO: 329)
13E7 (SST20 2443)	EIVMTQSPATLSVSPGERATLSCRAS QSVSSNLAWFQQKPGQAPRLLIYGA STRATGIPARFSGSGSGTEFTLTISL QPEDFAVYYCLQDNNFPPTFGQGTK VDIK (SEQ ID NO: 330)	EVQLVQSGAEVKKPGESLKISC KSGYSFTSYWIGWVRQMPGK GLEWMGIIYPGDADARYSPSFQ GQVTISADKSISTAYLQWSSLKA SDTAMYFCARRRQGIFGDALDF WGQGTLLVTVSS (SEQ ID NO: 331)
5E3 (SST29 825)	DIQMTQSPSSLSASVGDRVITICRAS QGISNYLAWYQQKPGKAPKSLIYAA SSLQSGVPSRFSGSGSGTDFTLTISL QPEDFATYYCQYSTYPPTFGQGTK VDIK (SEQ ID NO: 332)	QVQLVQSGAEVKKPGASVKVS CKASGYTFTGYYIHWRQAPGQ GLEWMGWINPYSGGTSAQKF QGRVTMTRDTSTSSAYMELSRL RSDDTAVYYCARDAGYLALYG TDVWGQGTLLVTVSS (SEQ ID NO: 333)

Table 20. Exemplary Variable Nucleotide Sequences of Engineered Antibodies

Ab ID.	LC variable region	HC variable region
24G6 (SST 2834 7 and SST2)	GACATCGTGATGACCCAGTCTCCAG ACTCCCTGGCTGTGTCTCTGGGCGA GAGGGCCACCATCAACTGCAAGTCC AGCCAGAGTGTTTTATACAGCTCCA ACAATAAGCACTTCTTAGCTTGGTA CCAGCAGAAACCAGGACAGCCTCCT	GAGGTGCAGCTGTTGGAGTCT GGGGGAGGCTTGGTACAGCCT GGGGGGTCCCTGAGACTCTCC TGTGCAGCCTCTGGATTACCT TTAGCAGCTATGCCATGAGCT GGGTCCGCCAGGCTCCAGGGA

0481 2)	AAGCTGCTCATTCTACTGGGCATCTA CCCGGGAGTCCGGGGTCCCTGACCG ATTCAGTGGCAGCGGGTCTGGGACA GATTTCACTCTCACCATCAGCAGCCT GCAGGCTGAAGATGTGGCAGTTTAT TACTGTCAGCAATATTATAGTACTCC GCTCACTTTCGGCGGAGGGACCAAG GTGGAGATCAAA (SEQ ID NO: 343)	AGGGACTGGAGTGGGTCTCAG CTATTAGTGGTAGTGGTGGTA GCACATACTACGCAGAATCCG TGAAGGGCCGGTTCACCATCT CCAGAGACAATTCCAAGAACA CGCTGTATCTGCAAATGAACA GCCTGAGAGCCGAGGACACGG CCGTATATTACTGTGCGAAGG CGTATACACCTATGGCATTCTT TGACTACTGGGGCCAGGGAAC CCTGGTCACCGTCTCCTCA (SEQ ID NO: 344)
6E7 (SST 2985 7)	GACATCCAGATGACCCAGTCTCCAT CTTCCGTGTCTGCATCTGTAGGAGA CAGAGTCACCATCACTTGTCGGGCG AGTCAGGGTATTAGCAGCTGGTTAG CCTGGTATCAGCAGAAACCAGGGAA AGCCCCCTAAGCTCCTGATCTATGCT GCATCCAGTTTGCAAAGTGGGGTCC CATCAAGGTTTCAGCGGCAGTGGATC TGGGACAGATTTCACTCTCACCATC AGCAGCCTGCAGCCTGAAGATTTTG CAACTTACTTTTGTCAACAGGCTGA CGCTTTCCTTCGCACTTTTGGCCAGG GGACCAAGCTGGAGATCAAA (SEQ ID NO: 345)	GAGGTGCAGCTGGTGCAGTCT GGAGCAGAGGTGAAAAAGCCC GGGGAGTCTCTGAAGATCTCC TGTAAGGGTTCTGGATACAGTT TTACCAGCTACTGGATCGCCTG GGTGCGCCAGATGCCCCGGGAA AGGCCTGGAGTGGATGGGGAT CATCTATCCTGGTGACGCTGAT GCCAGATACAGCCCGTCCTTCC AAGGCCAGGTCACCATCTCAG CCGACAAGTCCATCAGCACCG CCTACCTACAGTGGAGCAGCC TGAAGGCCTCGGACACCGCCA TGTATTTCTGTGCGAGACAAA GGACGTTTTATTATGATAGTAG TGATTATTTTGACTACTGGGGC CAGGGAACCCTGGTCACCGTG TCCTCA (SEQ ID NO: 346)
13E7 (SST	GAAATAGTGATGACGCAGTCTCCAG CCACCCTGTCTGTGTCTCCAGGGGA AAGAGCCACCCTCTCCTGCAGGGCC	GAGGTGCAGCTGGTGCAGTCT GGAGCAGAGGTGAAAAAGCCC GGGGAGTCTCTGAAGATCTCC

2024 43)	AGTCAGAGTGTAGCAGCAACTTAG CCTGGTTCCAGCAGAAACCTGGCCA GGCTCCCAGGCTCCTCATCTATGGT GCTTCCACCAGGGCCACTGGTATTC CAGCCAGGTTTCAGTGGCAGTGGGTC TGGGACAGAGTTCACTCTCACCATC AGCAGCCTGCAGCCTGAAGATTTTG CAGTTTATTACTGTCTGCAGGATAAT AATTTCCCTCCCCTTTTCGGCCAAGG GACCAAAGTGGATATCAAA (SEQ ID NO: 347)	TGTAAGGGTTCTGGATACAGC TTTACCAGCTACTGGATCGGCT GGGTGCGCCAGATGCCCCGGA AAGGCCTGGAGTGGATGGGGA TCATCTATCCTGGAGATGCTGA TGCCAGATACAGCCCGTCCTTC CAAGGCCAGGTCACCATCTCA GCCGACAAGTCCATCAGCACC GCCTACCTGCAGTGGAGCAGC CTGAAGGCCTCGGACACCGCC ATGTATTTCTGTGCGAGGCGG AGACAGGGGATCTTCGGTGAT GCTCTTGATTTCTGGGGCCAAG GGACATTGGTCACCGTGTCTTC A (SEQ ID NO: 348)
5E3 (SST 2982 5)	GACATCCAGATGACCCAGTCTCCAT CCTCACTGTCTGCATCTGTAGGAGA CAGAGTCACCATCACTTGTCGGGCG AGTCAGGGCATTAGCAATTATTTAG CCTGGTATCAGCAGAAACCAGGGAA AGCCCCTAAATCCCTGATCTATGCT GCATCCAGTTTGCAAAGTGGGGTCC CATCAAGGTTTCAGCGGCAGTGGATC TGGGACAGATTTCACTCTCACCATC AGCAGCCTGCAGCCTGAAGATTTTG CAACTTATTACTGCCAACAGTATAG TACTTACCCATTCACTTTTCGGCCAAG GGACCAAAGTGGATATCAAA (SEQ ID NO: 349)	CAGGTGCAGCTGGTGCAGTCT GGGGCTGAGGTGAAGAAGCCT GGGGCCTCAGTGAAGGTGTCC TGCAAGGCTTCTGGATACACCT TCACCGGCTACTATATCCACTG GGTGCGACAGGCCCCTGGACA AGGGCTTGAGTGGATGGGATG GATCAACCCTTACAGTGGTGG CACAACCTCTGCACAGAAGTT TCAGGGCAGGGTCACCATGAC CAGGGACACGTCCACCAGCTC AGCCTACATGGAAGTGAAGCAG GCTGAGATCTGACGACACGGC CGTGTATTACTGTGCGAGAGA TGCAGGCTACCTGGCCCTCTAC GGTACGGACGTCTGGGGCCAA GGGACCTTGGTCACCGTGTCTTC CA (SEQ ID NO: 350)

[0287] Select anti-TREM2 antibodies, which were isolated from hybridomas as human IgG2 antibodies, were converted to human IgG1 antibodies or aglycosylated variants of human IgG1 antibodies (mutations N297G, R292C, V302C according to EU numbering) by transferring the variable regions of the antibodies onto human IgG1 constant regions. The IgG1-type antibodies were evaluated for agonist activity using the AlphaLISA pSyk activation assay described in Example 2. Surprisingly, conversion of these select antibodies from an IgG2 isotype to an IgG1 isotype resulted in a partial loss of agonist activity (Figure 7).

[0288] The unique arrangement of the disulfide bonds in the hinge region of IgG2 antibodies has been reported to impart enhanced stimulatory activity for certain anticancer antibodies (White *et al.*, Cancer Cell, Vol. 27: 138-148, 2015). This enhanced activity could be transferred to IgG1-type antibodies by exchanging the CH1 and hinge regions of the IgG1 antibody for those in the IgG2 antibody (White *et al.*, 2015).

[0289] To evaluate whether the agonist activity of the 24G6, 6E7 and 5E3 anti-TREM2 IgG2 antibodies could be enhanced or retained when converted to IgG1 isotypes, constructs were made in which the heavy chain variable region sequences from each of the 24G6, 6E7 and 5E3 antibodies were inserted in frame to sequences encoding the CH1 and hinge regions from a human IgG2 antibody and sequences encoding the Fc region (CH2 and CH3 regions) from an aglycosylated human IgG1 antibody. The aglycosylated human IgG1 antibody Fc region comprised the sequence of a human IgG1z Fc region with N297G, R292C, and V302C mutations according to EU numbering (SEQ ID NO: 282).

[0290] In addition to replacing the CH1 and hinge regions of the IgG1 antibodies with those from the IgG2 antibodies, point mutations were made at specific residues within the hinge and CH1 regions to lock the antibodies into a particular disulfide bond configuration. It has been reported that the disulfide bonds in the hinge and CH1 regions of IgG2 antibodies can be shuffled to create different structural disulfide isoforms (IgG2A, IgG2B, and IgG2A-B) and these different disulfide isoforms can have different levels of activity. *See, e.g.*, Dillon *et al.*, J. Biol. Chem., Vol. 283: 16206-16215; Martinez *et al.*, Biochemistry, Vol. 47: 7496-7508, 2008; and White *et al.*, Cancer Cell, Vol. 27: 138-148, 2015. To lock the hinge-modified IgG1 antibodies into a IgG2B disulfide configuration, two sets of point mutations were made: (1) a C127S mutation according to Kabat numbering (C131S according to EU numbering) in the heavy chain and (2) a C214S mutation in the light chain combined with a

C233S mutation in the heavy chain, both according to Kabat numbering (C214S and C220S according to EU numbering). *See, e.g.,* WO 2009/036209, which is hereby incorporated by reference in its entirety. The IgG2-hinge modified IgG1 versions of the 6E7 and 5E3 antibodies containing the additional point mutations are expected to show equivalent or superior agonist activity in the AlphaLISA pSyk activation assay as the parental IgG2 molecules.

Table 21. Light Chain and Heavy Chain Amino Acid Sequences of Exemplary Antibodies

Ab ID.		Sequence
24G6 (SST28347)	LC	MDMRVPAQLLGLLLLWLRGARCDIVMTQSPDSLAVSLGERA TINCKSSQSVLYSSNNKHFLAWYQQKPGQPPKLLIYWASTRE SGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTPLTF GGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYP REAKVQWKVDNALQSGNSQESVTEQDSKSTYSLSSLTLS KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 334)
	HC	MDMRVPAQLLGLLLLWLRGARCEVQLLES GGGLVQP GGSL RLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTY YAESVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKAY TPMAFFDYWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTTPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK (SEQ ID NO: 335)
24G6 (SST204812)	LC	MDMRVPAQLLGLLLLWLRGARCDIVMTQSPDSLAVSLGERA TINCKSSQSVLYSSNNKHFLAWYQQKPGQPPKLLIYWASTRE SGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTPLTF GGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYP REAKVQWKVDNALQSGNSQESVTEQDSKSTYSLSSLTLS

Ab ID.		Sequence
		KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 334)
	HC	MDMRVPAQLLGLLLLWLRGARCEVQLLES GGGLVQPGGSL RLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTY YAESVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKAY TPMAFFDYWGQGT LVTVSSASTKGPSVFPLAPSSRSTSESTA ALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSNFGTQTYTCNV DHKPSNTKVDKTVERKCCVECP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHED PEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL P PSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK (SEQ ID NO: 336)
6E7 (SST29857)	LC	MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSVSASVGDRV TITCRASQGISSWLAWYQQKPGKAPKLLIYAASSLQSGVPSRF SGSGSGTDFTLT ISSLQPEDFATYFCQQADAFPRFTFGQGTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 337)
	HC	MDMRVPAQLLGLLLLWLRGARCEVQLVQSGAEVKKPGESL KISCKGSGYSFTSYWIAWVRQMPGKGLEWMGHIYPGDADAR YSPSFQGGVTISADKSISTAYLQWSSLKASDTAMYFCARQRT FYYDSSDYFDYWGQGT LVTVSSASTKGPSVFPLAPSSRSTSES TAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSNFGTQTYTCNV DHKPSNTKVDKTVERKCC VECPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDV SHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTTPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK (SEQ ID NO: 338)

Ab ID.		Sequence
13E7 (SST202443)	LC	MDMRVPAQLLGLLLLWLRGARCEIVMTQSPATLSVSPGERA TLSCRASQSVSSNLAWFQQKPGQAPRLLIYGASTRATGIPARF SGSGSGTEFTLTISLQPEDFAVYYCLQDNNFPPTFGQGTKVD IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSYSTLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 339)
	HC	MDMRVPAQLLGLLLLWLRGARCEVQLVQSGAEVKKPGESL KISCKGSGYSFTSYWIGWVRQMPGKGLEWMGHIYPGDADAR YSPSFQGGVTISADKSISTAYLQWSSLKASDTAMYFCARRRQ GIFGDALDFWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVS HEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTTPVLDSGDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK (SEQ ID NO: 340)
5E3 (SST29825)	LC	MDMRVPAQLLGLLLLWLRGARCIDIQMTQSPSSLSASVGDRV TITCRASQGISNYLAWYQQKPGKAPKSLIYAASSLQSGVPSRF SGSGSGTDFTLTISLQPEDFATYYCQQYSTYPFTFGQGTKVD IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSYSTLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 341)
	HC	MDMRVPAQLLGLLLLWLRGARCQVQLVQSGAEVKKPGASV KVSCKASGYTFTGYYIHWVRQAPGQGLEWMGWINPYSGGT TSAQKFQGRVTMTRDTSTSSAYMELSRLRSDDTAVYYCARD AGYLALYGTDVWGQGTLVTVSSASTKGPSVFPLAPSSRSTSE STAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTKVERKCC VECPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDV SHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLT

Ab ID.	Sequence
	VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTTPVLDSDGSEFLYSKLTVDKSRWQQGNVFSVSMHEA LHNHYTQKSLSLSPGK (SEQ ID NO: 342)

Table 22. Light Chain and Heavy Chain Nucleotide Sequences of Exemplary Antibodies

Ab ID.		Sequence
24G6 (SST28347)	LC	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGC TGCTGTGGCTGAGAGGTGCGCGCTGTGACATCGTGATGAC CCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGG GCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATACA GCTCCAACAATAAGCACTTCTTAGCTTGGTACCAGCAGAA ACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCT ACCCGGGAGTCCGGGGTCCCTGACCGATTCACTGGCAGCG GGTCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCA GGCTGAAGATGTGGCAGTTTATTACTGTCAGCAATATTAT AGTACTCCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGA TCAAACGAACGGTGGCTGCACCATCTGTCTTCATCTTCCCG CCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGT GTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTA CAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCC AGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCT ACAGCCTCAGCAGCACCCCTGACGCTGAGCAAAGCAGACTA CGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAG GGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAG AGTGT (SEQ ID NO: 351)
	HC	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGC TGCTGTGGCTGAGAGGTGCGCGCTGTGAGGTGCAGCTGTT GGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG AGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCAGCTA TGCCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGACTG GAGTGGGTCTCAGCTATTAGTGGTAGTGGTGGTAGCACAT

Ab ID.		Sequence
		ACTACGCAGAATCCGTGAAGGGCCGGTTCACCATCTCCAG AGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC CTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAAGG CGTATACACCTATGGCATTCTTTGACTACTGGGGCCAGGG AACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCA TCGGTCTTCCCCCTGGCACCTCCTCCAAGAGCACCTCTGG GGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTC CCCGAACCGGTGACGGTGTCTGTGGAACCTCAGGCGCCCTGA CCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTC AGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCC AGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATC ACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGC CCAAATCTTGTGACAAACTCACACATGCCCACCGTGCCC AGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCC CCCCCAAACCAAGGACACCCTCATGATCTCCCGGACCCC TGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGAC CCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGG TGCATAATGCCAAGACAAAGCCGTGCGAGGAGCAGTACG GCAGCACGTACCGTTGCGTCAGCGTCCTCACCGTCCTGCA CCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGT GTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATC TCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTAC ACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCG ACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGA ACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGG CTCCTTCTTCCTCTATAGCAAGCTCACCGTGAGACAAGAGC AGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGC ATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTC CCTGTCTCCGGGCAA (SEQ ID NO: 352)
24G6 (SST204812)	LC	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGC TGCTGTGGCTGAGAGGTGCGCGCTGTGACATCGTGATGAC

Ab ID.	Sequence
	CCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGG GCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATACA GCTCCAACAATAAGCACTTCTTAGCTTGGTACCAGCAGAA ACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCT ACCCGGGAGTCCGGGGTCCCTGACCGATTTCAGTGGCAGCG GGTCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCA GGCTGAAGATGTGGCAGTTTATTACTGTCAGCAATATTAT AGTACTCCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGA TCAAACGAACGGTGGCTGCACCATCTGTCTTCATCTTCCCG CCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGT GTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTA CAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCC AGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCT ACAGCCTCAGCAGCACCCCTGACGCTGAGCAAAGCAGACTA CGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAG GGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAG AGTGT (SEQ ID NO: 351)
HC	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGC TGCTGTGGCTGAGAGGTGCGCGCTGTGAGGTGCAGCTGTT GGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG AGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAGCTA TGCCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGACTG GAGTGGGTGTCAGCTATTAGTGGTAGTGGTGGTAGCACAT ACTACGCAGAATCCGTGAAGGGCCGGTTCACCATCTCCAG AGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC CTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAAGG CGTATACACCTATGGCATTCTTTGACTACTGGGGCCAGGG AACCCTGGTCACCGTGTCTCAGCCTCCACCAAGGGCCCA TCGGTCTTCCCCCTGGCGCCCAGCTCCAGGAGCACCTCCG AGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTT CCCCGAACCGGTGACGGTGTCTGGAAGTCAAGGCGCTCTG ACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCT

Ab ID.		Sequence
		CAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTC CAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGAT CACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAG CGCAAATGTTGTGTCGAGTGCCCAACCGTGCCAGCACCTG AACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCAA ACCCAAGGACACCTCATGATCTCCCGGACCCCTGAGGTC ACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAG GTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATA ATGCCAAGACAAAGCCGTGCGAGGAGCAGTACGGCAGCA CGTACCGTTGCGTCAGCGTCCTCACCGTCCTGCACCAGGA CTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTGTCCAAC AAAGCCCTCCCAGCCCCATCGAGAAAACCATCTCCAAAG CCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCC CCCATCCCGGGAGGAGATGACCAAGAACCAGGTGAGCCT GACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCC GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTAC AAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTT CCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAG CAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTC TGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCC GGGCAA (SEQ ID NO: 353)
6E7 (SST29857)	LC	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGC TGCTGTGGCTGAGAGGTGCGCGCTGTGACATCCAGATGAC CCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGA GTCACCATCACTTGTCGGGCGAGTCAGGGTATTAGCAGCT GGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCC CATCAAGGTTTCAGCGGCAGTGGATCTGGGACAGATTTTAC TCTACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTT ACTTTTGTCAACAGGCTGACGCTTTCCCTCGCACTTTTGGC CAGGGGACCAAGCTGGAGATCAAACGAACGGTGGCTGCA CCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAA

Ab ID.	Sequence
	ATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCT ATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACG CCCTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCA GGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTT GACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTA CGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTC ACAAAGAGCTTCAACAGGGGAGAGTGT (SEQ ID NO: 354)
HC	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGC TGCTGTGGCTGAGAGGTGCGCGCTGTGAGGTGCAGCTGGT GCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAGTCTCT GAAGATCTCCTGTAAGGGTTCTGGATACAGTTTTACCAGC TACTGGATCGCCTGGGTGCGCCAGATGCCCGGGAAAGGCC TGGAGTGGATGGGGATCATCTATCCTGGTGACGCTGATGC CAGATACAGCCCGTCCTTCCAAGGCCAGGTCACCATCTCA GCCGACAAGTCCATCAGCACCGCCTACCTACAGTGGAGCA GCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGCGAG ACAAAGGACGTTTTATTATGATAGTAGTGATTATTTGACT ACTGGGGCCAGGGAACCCTGGTCACCGTGTCTCAGCCTC CACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCAGCTCC AGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGG TCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGGAA CTCAGGCGCTCTGACCAGCGGCGTGACACCTTCCCAGCT GTCCTACAGTCTCAGGACTCTACTCCCTCAGCAGCGTGGT GACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACC TGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGAC AAGACAGTTGAGCGCAAATGTTGTGTGAGTGCCACCGT GCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCT CTTCCCCC AAAACCAAGGACACCCTCATGATCTCCCGG ACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGCCACG AAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGT GGAGGTGCATAATGCCAAGACAAAGCCGTGCGAGGAGCA GTACGGCAGCACGTACCGTTGCGTCAGCGTCCTCACCGTC

Ab ID.		Sequence
		CTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGC AAGGTGTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAA CCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGG TGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAA CCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCC AGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCG GAGAACAACCTACAAGACCACGCCTCCCGTGCTGGACTCCG ACGGCTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAA GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTG ATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCC TCTCCCTGTCTCCGGGCAA (SEQ ID NO: 355)
13E7 (SST202443)	LC	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGC TGCTGTGGCTGAGAGGTGCGCGCTGTGAAATAGTGATGAC GCAGTCTCCAGCCACCCTGTCTGTGTCTCCAGGGGAAAGA GCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCA ACTTAGCCTGGTTCCAGCAGAAACCTGGCCAGGCTCCCAG GCTCCTCATCTATGGTGCTTCCACCAGGGGCCACTGGTATTC CAGCCAGGTTCAAGTGGCAGTGGGTCTGGGACAGAGTTCAC TCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAGTTT ATTACTGTCTGCAGGATAATAATTTCCCTCCCCTTTTCGGC CAAGGGACCAAAGTGGATATCAAACGAACGGTGGCTGCA CCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAA ATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCT ATCCCAGAGAGGGCAAAGTACAGTGGAAGGTGGATAACG CCCTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCA GGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTT GACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTA CGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTC ACAAAGAGCTTCAACAGGGGAGAGTGT (SEQ ID NO: 356)
	HC	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGC TGCTGTGGCTGAGAGGTGCGCGCTGTGAGGTGCAGCTGGT GCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGGAGTCTCT

Ab ID.	Sequence
	GAAGATCTCCTGTAAGGGTTCTGGATACAGCTTTACCAGC TACTGGATCGGCTGGGTGCGCCAGATGCCCCGGGAAAGGCC TGGAGTGGATGGGGATCATCTATCCTGGAGATGCTGATGC CAGATACAGCCCCGTCCTTCCAAGGCCAGGTCAACCATCTCA GCCGACAAGTCCATCAGCACCGCCTACCTGCAGTGGAGCA GCCTGAAGGCCTCGGACACCGCCATGTATTTCTGTGCGAG GCGGAGACAGGGGATCTTCGGTGATGCTCTTGATTTCTGG GGCCAAGGGACATTGGTCAACCGTGTCTTCAGCCTCCACCA AGGGCCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAG CACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAG GACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACCTCAG GCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCCT ACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACC GTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCA ACGTGAATCACAAAGCCCAGCAACACCAAGGTGGACAAGA AAGTTGAGCCCCAAATCTTGTGACAAAACCTCACACATGCCC ACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTC TTCCTCTTCCCCC AAAACCCAAGGACACCCTCATGATCTC CCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGC CACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACG GCGTGGAGGTGCATAATGCCAAGACAAAGCCGTGCGAGG AGCAGTACGGCAGCACGTACCGTTGCGTCAGCGTCCTCAC CGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAG TGCAAGGTGTCCAACAAAGCCCTCCCAGCCCCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCAC AGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAA GAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTAT CCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG CCGGAGAACAACCTACAAGACCACGCCTCCCGTGCTGGACT CCGACGGCTCCTTCTTCCTCTATAGCAAGCTCACCGTGGAC AAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCG

Ab ID.		Sequence
		TGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAG CCTCTCCCTGTCTCCGGGCAAA (SEQ ID NO: 357)
5E3 (SST29825)	LC	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGC TGCTGTGGCTGAGAGGTGCGCGCTGTGACATCCAGATGAC CCAGTCTCCATCCTCACTGTCTGCATCTGTAGGAGACAGA GTCACCATCACTTGTCTGGGCGAGTCAGGGCATTAGCAATT ATTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA ATCCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCC CATCAAGGTTTCAGCGGCAGTGGATCTGGGACAGATTTAC TCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTT ATTACTGCCAACAGTATAGTACTTACCCATTCACTTTTCGGC CAAGGGACCAAAGTGGATATCAAACGAACGGTGGCTGCA CCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAA ATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCT ATCCCAGAGAGGGCCAAAGTACAGTGGAAGGTGGATAACG CCCTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCA GGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTT GACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTA CGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTC ACAAAGAGCTTCAACAGGGGAGAGTGT (SEQ ID NO: 358)
	HC	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGC TGCTGTGGCTGAGAGGTGCGCGCTGTGAGGTGCAGCTGGT GCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTG AAGGTGTCCTGCAAGGCTTCTGGATACACCTTCACCGGCT ACTATATCCACTGGGTGCGACAGGCCCTTGACAAAGGGCT TGAGTGGATGGGATGGATCAACCCTTACAGTGGTGGCACA ACCTCTGCACAGAAGTTTCAGGGCAGGGTCACCATGACCA GGGACACGTCCACCAGCTCAGCCTACATGGAAGTGGAGCAG GCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGA GATGCAGGCTACCTGGCCCTCTACGGTACGGACGTCTGGG GCCAAGGGACCTTGGTCACCGTGTCTCAGCCTCCACCAA GGGCCCATCGGTCTTCCCCCTGGCGCCCAGCTCCAGGAGC

Ab ID.	Sequence
	ACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGG ACTACTTCCCCGAACCGGTGACGGTGTCTGGAAGTCAAGG CGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTA CAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCG TGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAA CGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGAC AGTTGAGCGCAAATGTTGTGTCGAGTGCCCAACCGTGCCCA GCACCTGAATCCTGGGGGGACCGTCAGTCTTCCTCTTCCC CCCAAACCCAAGGACACCCCTCATGATCTCCCGGACCCCT GAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGAC CCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGG TGCATAATGCCAAGACAAAGCCGTGCGAGGAGCAGTACG GCAGCACGTACCGTTGCGTCAGCGTCCTCACCGTCCTGCA CCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGT GTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATC TCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTAC ACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCG ACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGA ACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGG CTCCTTCTTCTCTATAGCAAGCTCACCGTGGACAAGAGC AGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGC ATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTC CCTGTCTCCGGGCAAA (SEQ ID NO: 359)

Example 8. Affinity Modulation of Agonist Anti-TREM2 Antibodies

[0291] To generate antibody variants with increased or decreased affinity for human TREM2, affinity modulation of the 6E7 agonist anti-TREM2 monoclonal antibody was performed using fluorescence-activated cell sorting (FACS) of yeast-displayed Fab libraries. An unbiased library construction strategy was used, where NNK saturation mutagenesis was completed for every amino acid residue of each light-chain and heavy-chain CDR to generate point mutations. A separate Fab library was generated for each CDR. The six yeast-displayed

Fab libraries were separately sorted and screened for variants with improved and reduced binding to human TREM2 using FACS. Secondary libraries that combined binding-enriched mutations through CDR and chain shuffling were also constructed, sorted, and screened.

Flow cytometry screening data for the 6E7 variants is shown in Table 19 below. The amino acid positions of the point mutations in the indicated regions of the 6E7 heavy and light chain variable regions are numbered with respect to the 6E7 heavy chain variable region sequence (SEQ ID NO: 124) and the 6E7 light chain variable region sequence (SEQ ID NO: 61).

Twenty-two variants were selected for further evaluation and characterization. The full heavy and light chain variable region sequences and associated CDRs for select variants having improved binding affinity relative to the 6E7 antibody are provided in Tables 2A and 2B, whereas the full heavy and light chain variable region sequences and associated CDRs for select variants having reduced binding affinity relative to the 6E7 antibody are provided in Tables 3A and 3B.

Table 23. 6E7 Antibody Affinity Modulation Variants

Variant Ab ID	Substitutions with respect to 6E7 VH sequence (SEQ ID NO: 124)			Substitutions with respect to 6E7 VL sequence (SEQ ID NO: 61)			Binding Signal (fold over 6E7 parental antibody)			
	HC FR1-CDR1	HC CDR2	HC CDR3	LC CDR1	LC CDR2	LC CDR3	1 st screen 110 nM or 10nM ^a	2 nd screen 2 nM	2 nd screen 10 nM	2 nd screen 100 nM
V1	Y32S		Q99S		Q55T	F94Y	1.68	1.29	1.92	
V2	Y27S	S56G	Q99S		L54R	S93R	2.55	2.23	2.90	
V3	T30A	G66D	Q99G		L54R	S93R	1.97	1.95	2.24	
V4	T30G	Y60V	Q99S		S53R	F94Y	6.00	5.88	5.51	
V5		I50T				F94H	2.73	1.25	2.84	
V6	Y32M						0.20*			0.56
V7	Y32E						0.11*			0.32
V8		R59K					0.28*			0.77
V9			T101G				0.67*			0.54
V10					A50S		0.76*			0.70
V11						D92A	0.79*			0.42
V12	S28E	T58V	Q99G		N56R		2.29	1.04	2.58	
V13	T30G	P62A	Q99G		N56G	F94M	1.31	1.15	1.35	
V14	T30G	S56Q	Q99G		S53R		4.71	2.57	4.64	
V15	T30A	I50T	Q99S		S53W	F94Y	5.23	4.72	4.78	

	Substitutions with respect to 6E7 VH sequence (SEQ ID NO: 124)			Substitutions with respect to 6E7 VL sequence (SEQ ID NO: 61)			Binding Signal (fold over 6E7 parental antibody)			
Variant Ab ID	HC FR1-CDR1	HC CDR2	HC CDR3	LC CDR1	LC CDR2	LC CDR3	1 st screen 110 nM or 10nM ^a	2 nd screen 2 nM	2 nd screen 10 nM	2 nd screen 100 nM
V16	F29M	S56G	Q99S		S53N		4.01	3.57	4.04	
V17	T30G		Q99S		L54R	F94S	5.37	4.22	5.51	
V18	W33H						0.17*			0.42
V19	Y32S						0.59*			0.48
V20		I50R					0.18*			0.52
V21			Y109F				0.76*			0.68
V22					A50R		0.30*			0.71
V23						R96L	0.40*			0.40
V24		T58V	Q99S		N56K	R96H	2.64	1.42	2.90	
V25	T30G	I50L	Q99S		Q55A	F94M	4.23	3.15	4.70	
V26	A35G	I50T	F102M, Y112A		N56R	F94Y	3.57	2.83	3.47	
V27		S61A	Q99S		N56R		5.50	5.67	5.69	
V28	T30Q	I50T	Y103F		N56S	F94L	3.08	2.63	3.61	
V29	T30K						1.53	0.84	1.67	
V30	Y27S						0.79*			0.72
V31		D57E					0.61*			0.73
V32		P62N					0.82*			0.89
V33			Y104G				0.23*			0.34
V34					N56D		0.34*			1.02
V35						D92Y	0.21*			0.29
V36	I34L		Q99S		L54R	F94Y	3.38	4.00	3.44	
V37	F29H	Q65A	Q99S		N56W	F94Y	3.46	3.69	3.49	
V38	T30G	T58V			L54R	F94H	4.34	3.44	4.36	
V39	T30G	S61N	Q99G		Q55V	F94S	6.15	5.11	5.81	
V40	T30G	T58V	F110S		N56L	S93R	4.48	3.41	4.16	
V41		I50T					1.74	0.58	1.72	
V42	Y32A						0.45*			0.41
V43		D57G					0.20*			0.33
V44		G54S					0.65*			0.52
V45				W32F			0.43*			0.53
V46					S53T		0.83*			0.96
V47						R96M	0.42*			0.47
V48	T30G	T58V	Q99M		N56T	F94L	2.42	2.30	2.54	
V49	T30N	I50T, Y60L	Q99S		L54R	F94Y	6.51	5.02	6.58	

	Substitutions with respect to 6E7 VH sequence (SEQ ID NO: 124)			Substitutions with respect to 6E7 VL sequence (SEQ ID NO: 61)			Binding Signal (fold over 6E7 parental antibody)			
Variant Ab ID	HC FR1-CDR1	HC CDR2	HC CDR3	LC CDR1	LC CDR2	LC CDR3	1 st screen 110 nM or 10nM ^a	2 nd screen 2 nM	2 nd screen 10 nM	2 nd screen 100 nM
V50	T30G	I50V	F110L		L54R	F94L	4.10	3.39	4.16	
V51		T58V	Q99G, Y112N		L54R		2.81	1.83	3.18	
V52	T30E		Q99G		N56R	S93R	3.00	1.78	3.09	
V53		S63H					1.25	0.66	1.17	
V54	Y32Q						0.55*			0.54
V55		R59I, F64H					0.24*			0.66
V56		S61Q					0.23*			0.59
V57				R24A			0.84*			0.85
V58					A50K		0.28*			0.68
V59						Q89M	0.19*			0.60
V60	S28H	T58V	F110S		N56R	Q89G	3.26	3.35	3.63	
V61	T30S	S61N	Q99G		Q55V	F94L	5.08	3.63	5.22	
V62	T30G	S61A	D108G		N56R	Q89G	2.49	1.87	2.89	
V63	T30R		Q99S		N56R	S93R	3.76	4.91	3.71	
V64	T30Q		Q99G		Q55A	F94Y	5.41	4.88	5.48	
V65			Q99S				2.05	1.29	2.75	
V66	Y27T						0.25*			0.74
V67		I50M					0.80*			0.84
V68			Y103R				0.44*			0.43
V69				W32Y			0.41*			0.40
V70					S52G		0.79*			0.84
V71						F94E	0.37*			0.48
V72	A35G		Q99G		Q55V	F94Y	3.64	2.50	4.01	
V73	T30G	S63G	Q99G		L54R	F94Y	5.12	4.17	5.44	
V74	T30A	T58V	Q99G		N56L		3.94	2.54	4.01	
V75			Q99G		N56A	F94Y	4.64	3.74	4.52	
V76	T30G	S63E	F110S		N56K		4.57	4.34	4.93	
V77					L54R		1.43	0.83	1.38	
V78	S28R						0.86*			1.11
V79		R59N					0.70*			0.52
V80			T101N				0.59*			0.50
V81				W32L			0.17*			0.23
V82					A51G		0.30*			0.79
V83						D92V	0.20*			0.29

Variant Ab ID	Substitutions with respect to 6E7 VH sequence (SEQ ID NO: 124)			Substitutions with respect to 6E7 VL sequence (SEQ ID NO: 61)			Binding Signal (fold over 6E7 parental antibody)			
	HC FR1-CDR1	HC CDR2	HC CDR3	LC CDR1	LC CDR2	LC CDR3	1 st screen 110 nM or 10nM ^a	2 nd screen 2 nM	2 nd screen 10 nM	2 nd screen 100 nM
V84	S28G		F110S		A50G		1.44	1.45	1.62	
V85	T30R	I50T	Q99S		L54R		5.41	5.41	5.37	
V86	T30G, I34L	Q65E	Q99S		L54R		4.80	5.17	5.02	
V87	T30R	T58V, S63D	Q99S		N56W		3.84	4.86	3.93	
V88	T30G				S53R, N56R	F94S	4.92	5.57	5.30	
V89						F94H	1.33	0.94	1.46	
V90	Y32E			S31R			0.33*			0.36
V91		G54D					0.25*			0.61
V92			Y103H				0.22*			0.65
V93				S31G			0.35*			1.05
V94					S52A		0.31*			0.87

^aBinding signal values marked with an * were obtained with the 110 nM Ab concentration, whereas the remaining values in the column were obtained with the 10 nM Ab concentration

Example 9. Rescue of Macrophage and Microglia Survival Defect by Agonist Anti-TREM2 Antibody

[0292] The R47H variant of human TREM2 has been associated with increased risk for late-onset Alzheimer's disease (Jonsson *et al.*, New England Journal of Medicine, Vol. 368: 107-116, 2013). To specifically target the *Trem2* gene without perturbing additional regulatory elements, a gene-editing based approach was used to generate *Trem2*^{-/-} or *Trem2*^{R47H} mice. The *Trem2*^{-/-} strain was generated by engineering a 5bp or 11bp deletion in exon 1 of the *Trem2* gene and *Trem2*^{R47H} strain was generated by engineering a point mutation at residue 47 in the mouse *Trem2* gene analogous to the human variant. Detailed qPCR analyses of brain homogenates from *Trem2*^{-/-} and *Trem2*^{R47H} mice confirmed a loss of the gene in the knockouts and *Trem2* expression comparable to wild-type age-matched controls for the *Trem2*^{R47H} mice (data not shown). No significant differences were observed in other *TREM* genes in the locus (*Trem1*, *Trem11*, and *Trem12*) under basal or LPS stimulated conditions in wild-type, *Trem2*^{-/-} or *Trem2*^{R47H} mice (data not shown).

[0293] To understand the effect of TREM2 changes on myeloid cells, the properties of TREM2^{-/-} bone marrow derived macrophages (BMDMs) and adult and neonatal microglia were compared with wild-type macrophages and microglia in limiting conditions of CSF-1. Consistent with recent studies on TREM2^{-/-} microglia and macrophages that suffer from a survival deficiency at low levels of CSF-1 (Wang *et al.*, Cell, Vol. 160; 1061-1071, 2015; Wu *et al.*, Journal of Experimental Medicine, Vol. 212: 681-697, 2015), reduced survival of BMDMs and microglia isolated from our TREM2^{-/-} mice was also observed confirming that they display TREM2-dependent behavior reported in other TREM2^{-/-} models (Figures 8A-8C). To determine if the R47H mutation also impacts the ability of myeloid cells to survive in challenge conditions, similar studies were performed on TREM2^{R47H} BMDMs and microglia. Interestingly, the TREM2^{R47H} BMDMs and microglia also exhibited poorer survival under similar culture conditions much like the TREM2^{-/-} BMDMs and microglia (Figure 8D-8F). However, the survival defects of TREM2^{R47H} BMDMs and microglia were less pronounced than the survival defects of TREM2^{-/-} BMDMs and microglia. Gene dosage-dependent effects on survival of both TREM2^{R47H} and TREM2^{-/-} myeloid cells were also observed, with the effects being far more pronounced in the knockout cells compared to the variant cells (data not shown). While the TREM2^{R47H} macrophages phenotype follow the same trend as TREM2^{-/-} macrophages, the phenotypes cannot be explained simply by a reduction in cell surface expression of R47H TREM2 since wild-type and TREM2^{R47H} BMDMs appeared to have comparable levels of surface TREM2 expression (data not shown). Overall, the results of these experiments support a loss-of-function for the R47H variant that mimics a loss of the TREM2 protein albeit with a phenotype that is less pronounced compared to the gene knockout.

[0294] Next, TREM2 activation was assessed in TREM2^{R47H} BMDMs. A commercially available rat anti-human/mouse TREM2 antibody (mAb17291; Rat IgG2b Clone #237920, R&D Systems) increased pSyk levels in both R47H and wild-type BMDMs as measured by Western Blot with the effect being more pronounced in the wild-type BMDMs (Figure 9A). The antibodies had no effect on the TREM2^{-/-} macrophages supportive of specific activation of TREM2 (Figure 9B). To determine if activation of TREM2/DAP12-mediated Syk signaling in macrophages can ameliorate the more downstream biological phenotypes, including reduced survival, TREM2^{R47H} BMDMs were treated with the anti-TREM2 agonist antibody (mAb17291 antibody) or isotype control and the cell confluence was monitored using Incucyte Xoom Imaging System. Strikingly, a rescue in cell survival of TREM2^{R47H}

BMDMs was observed when the macrophages were treated with the anti-TREM2 agonist antibody with almost a complete restoration to wild-type levels (Figures 10A-10C). The significant boost in cell survival was observed both in live time-lapse imaging (Figures 10A and 10B) and endpoint cell viability (ATP accumulation) assays (Figure 10C). An equivalent rescue in cell survival was not observed when the BMDMs were treated with isotype controls antibodies (Figures 10A-10C). No increase in survival of homozygous TREM2 knockout macrophages was observed confirming that the effect is specific for TREM2 activation by the antibody (data not shown). A similar rescue of cell survival was observed for adult TREM2^{R47H} microglia when treated with the same anti-TREM2 agonist antibody, whereas an equivalent rescue in cell survival was not observed when the microglia were treated with an isotype control antibody (Figure 10D).

[0295] In addition, an anti-TREM2 agonist antibody (Antibody 2) that activated Syk signaling but did not compete with the commercial antibody boosted survival of macrophages harvested from aged (18-month old) wildtype and R47H animals (Figures 10E and 10F), whereas an equivalent rescue in cell survival was not observed when the microglia were treated with an isotype control antibody (Figures 10E and 10F).

[0296] To evaluate the effect of anti-TREM2 agonist antibody treatment on migration of wild-type, TREM2 knockout and TREM2^{R47H} myeloid cells, bone marrow derived macrophages isolated from mice of each of the different genotypes were assessed in a migration assay. Day 5 BMDMs from TREM2^{+/+}, TREM2^{R47H} and TREM2^{-/-} mice were harvested and seeded into Radius™ 96-well Migration Assay plates (Cell Biolabs) in complete RPMI media supplemented with 50 ng/ml M-CSF. The cells were treated with anti-TREM2 agonist antibody (Antibody 1 or Antibody 2), isotype control antibody, or vehicle for 24 hours. The cells were washed the next day following manufacturer's protocol to remove the Biocompatible Gel layer and expose the cell-free area for migration. The media was replaced with fresh growth media supplemented with 50 ng/ml M-CSF and anti-TREM2 agonist antibody, isotype control antibody, or vehicle control as above. The cell confluence was monitored using Incucyte Zoom Imaging System and data was plotted as percent confluence. Interestingly, treatment with Antibody 1 resulted in a small but statistically significant reduction in proliferation/migration of TREM2^{R47H} macrophages (Figure 11B) with minimal effects on wildtype macrophages (TREM2^{+/+}) (Figure 11A) and no effect on macrophages from the knockout mice (TREM2^{-/-}) (Figure 11C). Treatment with Antibody 2

had no effect on migration on either wildtype (TREM2^{+/+}) or TREM2^{R47H} macrophages (Figures 11D and 11E).

[0297] At the molecular level, this reduction in macrophage migration was reflected by a reduction in cell surface FLT1 in TREM2^{R47H} and wild-type macrophages upon anti-TREM2 agonist antibody treatment (both with and without treatment with lipopolysaccharide), whereas no significant differences in other chemokine/chemokine receptors (e.g. CCR5) were noted at the time points selected for the study (data not shown). The consistent correlation between migration and FLT1 both across different genotypes as well as with pharmacologic manipulation with an antibody speaks to an exciting novel link between TREM2 and FLT1 that will need further investigation. Equally interesting though is the observation that an antibody that activates TREM2/DAP12 signaling proximally can have opposing effects on survival and migration; different antibodies (depending on where they bind and how they interact with endogenous ligands) likely will have different proximal and distal activity profiles.

[0298] The results of these experiments demonstrate that an antibody that can activate TREM2/DAP12 signaling can rescue the viability defect of macrophages and microglia resulting from a loss of function mutation in TREM2. The results suggest that an agonist antibody that can activate TREM2 and boost macrophage/microglia activity may be therapeutic in Alzheimer's disease and other conditions associated with TREM2 loss of function.

Example 10. Gene Regulation by Agonist Anti-TREM2 Antibody in Macrophages

[0299] In order to understand the basis of the phenotypic changes of the macrophages derived from TREM2^{-/-} and TREM2^{R47H} mice described in Example 9 at the level of the transcriptome, RNA-Seq analyses were performed comparing wild-type, TREM2^{-/-} and TREM2^{R47H} macrophages at day 7 under limiting conditions of CSF-1. Day 7 BMDMs were harvested and total RNA was isolated using Rneasy Mini Kit (Qiagen) according to the manufacturer's protocol.

[0300] 1-2 µg of total RNA purified from bone marrow-derived *ex vivo* macrophages was used for cDNA library preparation by using a modified protocol based on the Illumina Truseq RNA Sample Preparation Kit (Illumina, San Diego, CA) and the published methods for strand-specific RNA-Seq (Perkins, T. T. *et al.*, PLoS genetics, Vol. 5: e1000569, 2009; Parkhomchuk, D. *et al.* Nucleic acids research, Vol. 37: e123, 2009). After poly-A selection,

fragmentation, and priming, reverse transcription was carried out for first strand cDNA synthesis in the presence of RNaseOut (Life Technologies, Carlsbad, CA) and actinomycin-D (MP Biomedicals, Santa Ana, CA). The synthesized cDNA was further purified by using AMPure RNAClean beads (Beckman Coulter, Pasadena, CA) following the commercial instruction. A modified method by incorporation of dUTP instead of dTTP was prepared and used for the second strand synthesis (Perkins *et al.*, PLoS genetics, Vol. 5, e1000569, 2009; Parkhomchuk *et al.*, Nucleic Acids Research, Vol. 37, e123, 2009). After AMPure XP bead purification (Beckman Coulter), following the standard protocol recommended by Illumina, end repairing, A-tailing, and ligation of index adaptors were sequentially performed for generation of cDNA libraries. After size selection of libraries using Pippin Prep (SAGE Biosciences, Beverly, MA), the dUTP-containing cDNA strands were destroyed by digestion of USER enzymes (New England Biolabs, Ipswich, MA) followed by a step of PCR enrichment for introduction of strand specificity. After cleaning up, the enriched cDNA libraries were analyzed in Agilent Bioanalyser and quantified by Quant-iT™ Pico-Green assays (Life Technologies) before being sequenced onto Illumina HiSeq platform. Each library generated at least 35 million of 75bp pair-end reads for downstream analysis.

[0301] RNA-seq sequencing reads were aligned using OSA aligner (Hu *et al.*, Bioinformatics, Vol. 28: 1933-1934, 2012) embedded in the Omicsoft ArrayStudio pipeline (Omicsoft Inc., USA). Mouse genome version GRCm38 and UCSC gene annotation were used in the alignment and quantification. Quantification was performed to the gene and transcript level based on RSEM (Li *et al.*, BMC Bioinformatics, Vol. 12: 323, 2011). Normalized gene expression level was calculated by fragments per kilobase per million reads (FPKM) then quantile normalized at 70 percentile to 10 (FPKQ). Only genes with at least one sample expressed at FPKQ ≥ 1 were used in the following statistical analysis. Raw reads counts from the selected genes were compared using R Bioconductor package DESeq2 following Negative Binomial distribution (Love *et al.*, Genome Biology, Vol. 15: 550, 2014). Genes with BH corrected p value < 0.05 and Fold Change ≥ 1.5 or $\leq 2/3$ were selected as significantly differentially expressed genes. Pathway analysis was performed using Ingenuity Pathway Analysis (IPA, QIAGEN Redwood City, USA).

[0302] Consistent with the gradation in severity of phenotypes observed across TREM2^{-/-}, TREM2^{R47H}, and wild-type macrophages, similar trends were observed in differentially regulated transcripts with the magnitude of effect being highest in the TREM2^{-/-} macrophages and TREM2^{R47H} macrophages falling in between wild-type and TREM2^{-/-} macrophages. This

differential regulation was confirmed for a subset of the genes in an independent experiment by qPCR (Figures 12A-12D). Pathway analyses point to a role for TREM2 in cell cycle, cell survival, cell proliferation and migration with cross-talk putatively between the complement pathway, lipid homeostasis and chemokines/receptors and migratory factors (data not shown).

[0303] Differences in transcript regulation over time were confirmed by qPCR for several genes, including some known genetic factors linked to Alzheimer's Disease, such as *ApoE* (Figures 13A and 13B), pro-inflammatory cytokines like *Il-1a* (Figures 13C and 13D), and a host of chemokines/chemokine receptors including *Cx3cr1* (Figures 13E and 13F), *Ccl5* (Figures 13K and 13L), *Ccl22* (Figures 13M and 13N), *Ccr5*, *Ccr2*, and *Ccl3* as well as complement genes including *Clqa* (Figures 13I and 13J) and *C3* (Figures 13O and 13P). In each instance, the effect was significantly more pronounced in TREM2^{-/-} macrophages compared to the TREM2^{R47H} macrophages. For the first time, a link between TREM2 and the pro-angiogenic receptor, *Vegfr1* (*Flt1*) was noted with a reduction of *Flt1* in TREM2^{-/-} and TREM2^{R47H} macrophages (Figures 13G and 13H). Additionally, an increase in VEGF-a in both TREM2^{-/-} and TREM2^{R47H} macrophages was observed consistent with a lack of receptor available for binding (data not shown). The reduction in multiple migratory factors results in a reduced migration/motility of TREM2^{-/-} and TREM2^{R47H} macrophages (Figures 14A and 14B). Recent studies have reported reduced numbers/migration of microglia in regions surrounding plaques and apoptotic cells in TREM2 knockouts (Mazaheri *et al.*, EMBO reports, e201743922, 2017; Wang *et al.*, Cell, Vol. 160: 1061-1071, 2015).

[0304] Consistent with the RNA seq. data, a reduction in the chemokine MCP-1/CCL2 secreted from TREM2^{-/-} and TREM2^{R47H} macrophages was also observed (Figure 15A). The reduced secretion of MCP-1/CCL2 by TREM2^{R47H} macrophages in challenge conditions could be restored with treatment with an agonist anti-TREM2 antibody (mAb17291 antibody)(Figure 15B). The ability of the agonist anti-TREM2 antibody to boost MCP-1/CCL2 along with improving myeloid survival (Example 9) is noteworthy and points to an overall improvement in different aspects of myeloid cell functioning with agonist antibody treatment. Further, when TREM2^{R47H} macrophages were treated with Abeta oligomers, an increase in MCP-1/CCL2 was observed that was further enhanced upon agonist anti-TREM2 antibody treatment (data not shown).

[0305] Agonist anti-TREM2 antibody treatment of TREM2^{R47H} macrophages also modulated gene expression in a direction opposite to the effect of the genotype and included genes involved in regulation of myeloid cell migration, proliferation, cell cycle and survival

(Figures 16A and 16B). Pathway analyses of the differentially regulated genes reveal a putative role for TREM2 in modulating different aspects of myeloid cell biology in challenge conditions including DNA replication, cell cycle regulation, proliferation, cell death and chemokine/cytokine modulation. In the context of Alzheimer's disease etiology, these transgenic data are supportive of the hypothesis that a deficit in TREM2, either in the form of a loss-of-function variant or reduced expression on the cell surface, contributes to a fundamental proliferation/survival deficit resulting in the subsequent inability to function efficiently with respect to phagocytosis of plaques/apoptotic cells, cytokine modulation or potentially novel barrier function. Additionally, the direct effect on reduced secretion of migratory chemokines like CCL2 and CCR2 also likely reduce the ability of macrophages/microglia to migrate efficiently towards apoptotic cells and plaques and can further contribute to increased plaque burden early on in disease course. The ability of an antibody that boosts proximal signaling to also rescue the viability defect and restore chemokine levels elegantly demonstrates the correlation between proximal functioning and more distal biology and is strongly supportive of a therapeutic antibody strategy that can potentially boost macrophage/microglia activity and be ameliorative in disease.

Example 11. Efficacy of Agonist Anti-TREM2 Antibody in EAE Model of Multiple Sclerosis

[0306] The efficacy of the agonist anti-TREM2 antibodies described herein in ameliorating symptoms and/or disease progression of multiple sclerosis is evaluated in the experimental autoimmune encephalitis (EAE) model of multiple sclerosis. EAE is induced in animals by myelin oligodendrocyte glycoprotein (MOG) and pertussis toxin as previously described in Feinstein *et al.*, Ann. Neurol., Vol. 51: 694-702, 2002. Briefly, groups of 7-9 week-old female TREM2 wild-type (C57BL/6 strain), TREM2^{-/-} and TREM2^{R47H} mice are injected subcutaneously with 100 µg of MOG peptide 35-55 (MEVGWYRSPFSRVVHLYRNGK (SEQ ID NO: 283)) emulsified in complete Freund's adjuvant containing 4 mg/mL of *Mycobacterium tuberculosis* H37RA. Pertussis toxin is injected intraperitoneally at 200 ng/mouse in 200 µL of saline on day 0 and day 2. Anti-TREM2 antibodies (30 mg/kg and 100 mg/kg) are dosed at days 0, 7 and 14 to determine the effect of antibody treatment at different points of time in disease progression. Multiple cytokines and inflammation endpoints including soluble TREM2, MCP-1/2, MIP1a and b, CCL2, CCR2 and additional chemokines/cytokines are measured in the periphery, CNS and CSF to assess the effect of the

anti-TREM2 antibodies. In addition, neurological impairment of the animals is evaluated by clinical score as follows: 0, no clinical signs of EAE; 1, limp tail; 2, flaccid tail and abnormal gait (ataxia and/or paresis of hind limbs); 3, severe hind limb paresis; 4, complete paralysis with hind body; and 5, moribund or death.

Example 12. Efficacy of Agonist Anti-TREM2 Antibody in Animal Models of Peritonitis and Sepsis

[0307] The effect of the agonist anti-TREM2 antibodies described herein in modulating the acute inflammatory response is evaluated in animal models of peritonitis and sepsis.

Zymosan, a polysaccharide cell wall component derived from *Saccharomyces cerevisiae*, can be injected into the peritoneal cavity of animals to reproduce the inflammatory response associated with peritonitis (see Cash *et al.*, Methods in Enzymology, Vol. 461: 379-396, 2009). Zymosan (1 mg/kg) is administered intraperitoneally concurrently or 24 hours following administration of anti-TREM2 antibodies (20 mg/kg), isotype control antibody, or vehicle. Plasma, CSF, CNS and peritoneal lavage fluid and macrophages are collected 4 and 24 hours post treatment. Multiple cytokines and inflammation endpoints, including a quantitative assessment of different myeloid cell types, as well as soluble TREM2, MCP-1/2, MIP1a and b, CCL2, CCR2 and additional chemokines/cytokines are measured in the periphery, CNS and CSF to assess the effect of the anti-TREM2 antibodies on the inflammatory response.

[0308] In a separate series of experiments, the effect of the agonist anti-TREM2 antibodies are evaluated in a lipopolysaccharide (LPS) model of gram negative bacterial sepsis. LPS (1 mg/kg) is administered intraperitoneally 24 hours after administration of anti-TREM2 antibodies (20 mg/kg), isotype control antibody, or vehicle. Plasma, CSF and CNS samples are collected 4 and 24 hours post treatment. Multiple cytokines and inflammation endpoints, including a quantitative assessment of different myeloid cell types, as well as soluble TREM2, MCP-1/2, MIP1a and b, CCL2, CCR2 and additional chemokines/cytokines are measured in the periphery, CNS and CSF to assess the effect of the anti-TREM2 antibodies on the inflammatory response.

Example 13. Epitope Mapping of Anti-TREM2 Antibodies

Immunoblot method for epitope mapping of anti-TREM2 antibodies

[0309] PepSpot peptides (JPT Peptide Technologies) to human soluble Trem2 were designed to cover the entire extracellular domain (beginning at histidine 21), generating 74 x 10 meric

linear peptides, including an additional 6 control peptides, for a total of 80 pepspots per cellulose membrane. The 10 mer peptide sequences were selected by walking along the protein by 2 amino acids, resulting in an overlap of 8 amino acids. Membranes were washed with 40 ml of 100 % methanol at room temperature for 10 minutes with gentle shaking, followed immediately with 3 washes of 40 ml TBST (TBS + 0.05% Tween 20) for 10 minutes each. Membranes were blocked with undiluted LICOR blocking buffer (Odyssey® Blocking Buffer 927-40000) overnight at room temperature with gentle shaking and incubated with 1 µg/ml 24G6 (PL-52705, Lot date 2.24.2017, [hu anti- $\langle$ huTrem2 $\rangle$ 21-191_24G6 VK4 (1-242) VL]:huKLC-CL + [hu anti- $\langle$ huTrem2 $\rangle$ 21-191_24G6 VH3 (1-471) VH]:huIgG1zSEFL2-2 (monoclonal antibody), iPS:536553, SS-28346) overnight at 40C with gentle shaking in Licor blocking buffer containing 1% Tween 20. The following day, blots were washed 4X with TBST Buffer (Tris Buffered Saline + 0.05% Tween 20) for 15 minutes each and probed with a secondary antibody (Licor cat # 925-32232 IRDye® 800CW Goat anti-human Lot# C70419-05) at a 1:20,000 dilution in Licor blocking buffer with with 1% Tween 20 and 0.1% SDS. The blots were incubated for 1 hour at room temperature with gentle shaking, protected from light, followed by another 4 washes in TBST and dried for 1 hour at room temperature. Western blot was scanned on the 800 channel using the Licor Odyssey infrared fluorescence imager.

MSD method for epitope mapping of anti-TREM2 antibodies

[0310] Peptides (sequences designed as previously described) were synthesized with biotin on the N-terminus (Sigma) to human soluble Trem2 and normalized to 20 mg/ml in 100% DMSO. MSD GOLD 96-Well Small Spot Streptavidin SECTOR plates (MSD#L45SA) were coated with the biotinylated peptides at 5 µg/ml in 2X PBS (- ca/-mg) pH 7.8-7.9 in 50 µl total volume per well and allowed to incubate at room temperature for 2 hours with gentle shaking. Plates were washed 3X with with TBST buffer (Tris buffered saline + 0.05% Tween-20, pH 7.2), 150 µl per well, using an automated plate washer. Monoclonal antibody 24G6.1 (PL-51585 Lot date 12/9/2016, hu anti- $\langle$ huTrem2 $\rangle$ IgG2, was labeled with MSD sulfo-tag as per manufacturer's SOP to serve as detection reagent and added at 1 µg/ml in MSD Diluent 100 (#R50AA-3), in a total volume of 25 µl per well. Plates were allowed to incubate for 1 hour at room temperature, with gentle shaking, then washed 3X with TBST buffer (Tris buffered saline + 0.05% Tween-20, pH 7.2), 150 µl per well, using an automated plate washer, flipped and washed for an additional 3 times. MSD Read Buffer T + surfactant

4x stock (#R92TC-3) was prepared by diluting to 1X with H₂O and adding 150 µl total volume per well. Plates were read immediately on MSD Sector 6000 reader.

Results

[0311] The 24G6 antibody was found to bind to the following peptides (HRDAGDLWFP (SEQ ID NO: 360), AGDLWFPGE (SEQ ID NO: 361) and GDLWFPGESE (SEQ ID NO: 362)). This provided data that 24G6 recognized the following peptide (HRDAGDLWFPGESE (SEQ ID NO: 363)) in TREM2. Alanine scanning of a slightly longer peptide PLDHRDAGDLWFPGESE (SEQ ID NO: 364) was also performed to identify key contact sites. 24G6 was found to show little to no binding to two alanine scanning peptides (PLDHRDAGDAWFPGESE (SEQ ID NO: 365); PLDHRDAGDLWAPGESE (SEQ ID NO: 366) (underlined amino acids)), suggesting those contacts were key for its recognition of this peptide. This work helped define the minimal peptide for recognition of human TREM2 by this antibody as GDLWFP (SEQ ID NO: 367). This antibody also demonstrated lower affinity to cynomolgus TREM2. Similar data was observed for peptides containing the corresponding cyno TREM2 sequence. For the other anti-TREM2 antibodies (6E7, 5E3 and 13E7), no specific peptides were identified that helped elucidate a peptide epitope using the described method.

Example 14. Peripheral Modulation of Agonist Anti-TREM2 Antibodies on Microglia Cells

[0312] In order to understand the effects of pharmacologic treatment on the global transcriptome, sc RNA-Seq studies were carried out on CNS resident Cd11b⁺ cells isolated from WT and R47H TREM2 mice dosed with the effectorless version of one of our agonist TREM2 antibodies. TREM2^{+/+}, TREM2^{-/-}, and TREM2^{R47H} male B6 mice (60-67 days old) were used for single-cell RNA-seq studies. Antibody treatment with either anti-murine TREM2 stable effector functionless (SEFL) antibody or anti-humanHer isotype control was administered intravenously at a dose of 30 mg/kg at 5 ml/kg. In the acute inflammation model, antibody-treated animals were given LPS (<source>) intraperitoneally 16 hours after antibody treatment at 5 mg/kg at 5 ml/kg and stimulated with LPS for 4 hours. The isotype control antibody in genotype-matched, age-matched and sex-matched littermate controls were simultaneously dosed.

[0313] Brains were harvested from treated mice following CO₂ asphyxiation and tissues were dissociated using the Miltenyi adult brain dissociation kit for mouse and rats (Miltenyi

Biotech 130-107-677) according to standard manufacturer's protocols. CD11b⁺ cells were positively enriched using microbeads (Miltenyi Biotec 130-049-601), washed twice in freshly prepared ice cold PBS + 0.04% BSA and resuspended in freshly PBS + 0.04% BSA at 500-1000 cells/ul at >70% viability. The brains were collected and microglia isolated using previously published Miltenyi's Cd11b isolation kit. NGS libraries were prepared as described per the 10x Chromium manufacturers' guidelines. Reverse transcription, total cDNA amplification, and library construction was performed according to manufacturer's protocol. Single-cell RNA sequencing was performed using the Chromium Single Cell 3' Kit with V2 Chemistry (10x Genomics). Enriched CD11b⁺ cells were loaded and encapsulated on the Chromium Single Cell Chip A (10x Genomics) to achieve a cell recovery of 5,000 cells per sample. A sequencing read depth of >2x of the Keren-Shaul et al. study, with roughly 2095 genes identified per cell and xUMIs per cell was achieved. T-distributed stochastic neighbor embedding (t-SNE) was applied to visualize single cell gene expression profiles and cells were grouped into cell types using dbSCAN clustering.

[0314] Eleven distinct populations were identified in total. The most dominant cluster of cells were as expected microglia as defined by a Trem2⁺, Tmem119⁺, P2ry12⁺, Hexb⁺, Lyz2⁺ gene signature, with microglial cells accounting for 60% of the total number of cells analyzed across all treatment groups and genotypes. Minor residual populations of endothelial cells, astrocytes, NK cells and oligodendrocytes that persisted after magnetic enrichment were also identified. The dominant microglial clusters distinctly separated out into two groups based on LPS treatment – a more homeostatic microglia cluster and an activated microglia cluster. Within the LPS activated state, the more subtle effects of the genotype differences (WT vs. R47H) and antibody treatment in both WT and R47H groups were observed. These patterns persisted even upon inspection of the microglia clusters alone. Additional smaller myeloid cell clusters that bore the hallmarks of microglial genes as well as classic infiltrate markers were also noted.

[0315] A careful analysis of the antibody treatment on the microglial clusters revealed that the antibody treatment had a few distinct biological effects. First, antibody treatment raised the level of homeostatic genes including Cx3cr1, Tmem119, Ctsd and P2ry12 in both WT and R47H microglia, WT microglia alone and R47H microglia alone (Figure 17 A, B and C). Second, antibody treatment decreased the transcript levels of pro-inflammatory chemokines and cytokines including Il1a, Il1b, Il27, Il12b, Ccr7, Ccl2, Ccl3, Ccl4 and Ccl5 (Figure 17 D, E and F). Thirdly, antibody treatment modulated several genes involved in Syk signaling

including several DUSPs (phosphatases that regulate Src kinases) and genes in the MAPK signaling pathway. Very few differences between WT and R47H microglia isolated from normal, unchallenged, 7-week old mice were observed.

[0316] In examining the differences between WT and R47H microglia in an unperturbed state as well as determining the effects of antibody treatment, we noted that in the LPS /antibody treated animals, about 15% of the cells that were clustered with the more traditional microglia groups bore a distinct gene signature with a higher representation from the R47H genotype. A careful analysis revealed that these cells first got clustered with the larger microglia group since they were *Trem2+*, *Tmem119+*, *Cx3cr1+* and *Hexb+*, classic markers used to define homeostatic microglia. Yet, these cells were also enriched for genes like *S100a8*, *Lcn2*, *S100a9*, *Camp*, *Hp*, *Cxcr2*, and *Il1r2* in both the WT and R47H populations compared to the larger, more classic microglial cluster. When we performed pathway analysis of the top genes that were preferentially expressed in this cluster, we found that these hits were associated with monocyte and neutrophil function (Figure 18 A and B). This group of infiltrate/microglia cells also responded to antibody treatment with a downregulation of the pro-inflammatory chemokines and cytokines from both WT and R47H KI, WT only and R47HKi only mice (Figure 18 C, D and E).

[0317] The data show that an acute dosing of the agonist antibody of the present invention in an LPS challenge model is adequate to positively regulate microglial function in the same way that constitutive gene over-expression does in a chronic indication like AD. In addition, specific activation of TREM2 by the agonist antibody of the invention impacts multiple homeostatic genes in an LPS treatment mode and restores a more homeostatic state overall.

[0318] All publications, patents, and patent applications discussed and cited herein are hereby incorporated by reference in their entireties. It is understood that the disclosed invention is not limited to the particular methodology, protocols and materials described as these can vary. It is also understood that the terminology used herein is for the purposes of describing particular embodiments only and is not intended to limit the scope of the appended claims.

[0319] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

[0320] The term “comprise” and variants of the term such as “comprises” or “comprising” are used herein to denote the inclusion of a stated integer or stated integers but not to exclude any other integer or any other integers, unless in the context or usage an exclusive interpretation of the term is required.

[0321] Any reference to any prior art in this specification is not, and should not be taken as an acknowledgement or any form of suggestion that the prior art forms part of the common general knowledge.

[0322] Definitions of the specific embodiments of the invention as claimed herein follow.

[0323] In a first aspect, the invention provides an anti-human TREM2 (hTREM2) antibody, comprising a light chain variable region having complementarity determining regions CDRL1, CDRL2, and CDRL3, and a heavy chain variable region having complementarity determining regions CDRH1, CDRH2, and CDRH3, wherein

CDRL1 comprises the amino acid sequence of: RASQSVSSNLA (SEQ ID NO:10);

CDRL2 comprises the amino acid sequence of: GASTRAT (SEQ ID NO:23);

CDRL3 comprises the amino acid sequence of: LQDNNFPPT (SEQ ID NO:368);

CDRH1 comprises the amino acid sequence of: SYWIG (SEQ ID NO:81);

CDRH2 comprises the amino acid sequence of: IIYPGDADARYSPSFQG (SEQ ID NO:369);

and

CDRH3 comprises the amino acid sequence of: RRQGIFGDALDF (SEQ ID NO:370).

[0324] In a second aspect, the invention provides an anti-human TREM2 (hTREM2) antibody, comprising a light chain variable region having the amino acid sequence of SEQ ID NO:330, and a heavy chain variable region having the amino acid sequence of SEQ ID NO:331.

[0325] In a third aspect, the invention provides an anti-human TREM2 (hTREM2) antibody, comprising a light chain having the amino acid sequence of:

EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWFQQKPGQAPRLLIYGASTRATGIPARFSGSG
SGTEFTLTISLQPEDFAVYYCLQDNNFPPTFGQGKVDIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEV
THQGLSPVTKSFNRGEC (SEQ ID NO:371); and

a heavy chain having the amino acid sequence of:

EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIYPGDADARYSPSF
 QGQVTISADKSISTAYLQWSSLKASDTAMYFCARRRQGIFGDALDFWGQGTLVTVSSASTKGPS
 VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP
 SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR
 TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
 K (SEQ ID NO:372).

[0326] In a fourth aspect, the invention provides a pharmaceutical composition comprising the anti-hTREM2 antibody of the first aspect and a pharmaceutically acceptable excipient.

[0327] In a fifth aspect, the invention provides a polynucleotide that encodes the anti-hTREM2 antibody of the first aspect.

[0328] In a sixth aspect, the invention provides an expression vector comprising the polynucleotide of the fifth aspect.

[0329] In a seventh aspect, the invention provides a host cell comprising the expression vector of the sixth aspect.

[0330] In an eighth aspect, the invention provides a method of producing an anti-hTREM2 antibody that specifically binds to human TREM2 comprising culturing the host cell of the seventh aspect in a culture medium under conditions that allow expression of the anti-hTREM2 antibody; and recovering the anti-hTREM2 antibody from the culture medium or host cell.

CLAIMS:

1. An anti-human TREM2 (hTREM2) antibody, comprising a light chain variable region having complementarity determining regions CDRL1, CDRL2, and CDRL3, and a heavy chain variable region having complementarity determining regions CDRH1, CDRH2, and CDRH3, wherein
CDRL1 comprises the amino acid sequence of: RASQSVSSNLA (SEQ ID NO:10);
CDRL2 comprises the amino acid sequence of: GASTRAT (SEQ ID NO:23);
CDRL3 comprises the amino acid sequence of: LQDNNFPPT (SEQ ID NO:368);
CDRH1 comprises the amino acid sequence of: SYWIG (SEQ ID NO:81);
CDRH2 comprises the amino acid sequence of: IIYPGDADARYSPSFQG (SEQ ID NO:369);
and
CDRH3 comprises the amino acid sequence of: RRQGIFGDALDF (SEQ ID NO:370).
2. The anti-hTREM2 antibody of claim 1, wherein the antibody is a chimeric antibody, a humanized antibody, or a fully human antibody.
3. The anti-hTREM2 antibody of claim 1 or claim 2, wherein the antibody is an IgG1, IgG2, IgG3, or IgG4 antibody.
4. The anti-hTREM2 antibody of claim 3, wherein the antibody is a human IgG1 antibody.
5. The anti-hTREM2 antibody of any one of claims 1 to 4, wherein the antibody comprises a mutation at amino acid position N297 according to EU numbering in its heavy chain.
6. The anti-hTREM2 antibody of claim 5, wherein the mutation is N297G.
7. The anti-hTREM2 antibody of any one of claims 1 to 4, wherein the antibody comprises R292C and V302C mutations according to EU numbering in its heavy chain.
8. An anti-human TREM2 (hTREM2) antibody, comprising a light chain variable region having the amino acid sequence of SEQ ID NO:330, and a heavy chain variable region having the amino acid sequence of SEQ ID NO:331.
9. The anti-hTREM2 antibody of claim 8, wherein the antibody is a human IgG1 antibody comprising a kappa light chain constant region.

10. The anti-hTREM2 antibody of claim 8 or claim 9, wherein the antibody comprises a mutation at amino acid position N297 according to EU numbering in its heavy chain.

11. The anti-hTREM2 antibody of claim 8 or claim 9, wherein the antibody comprises mutations R292C, N297G, and V302C according to EU numbering in its heavy chain.

12. An anti-human TREM2 (hTREM2) antibody, comprising a light chain having the amino acid sequence of:

EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWFQQKPGQAPRLLIYGASTRATGIPARFSGSG
SGTEFTLTISLQPEDFAVYYCLQDNNFPPTFGQGKVDIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPPREKAVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV
THQGLSSPVTKSFNRGEC (SEQ ID NO:371); and

a heavy chain having the amino acid sequence of:

EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIYPGDADARYSPSF
QGQVTISADKSISTAYLQWSSLKASDTAMYFCARRRQGIFGDALDFWGQGLTVTVSSASTKGPS
VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP
SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR
TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
K (SEQ ID NO:372).

13. A pharmaceutical composition comprising the anti-hTREM2 antibody of any one of claims 1 to 12 and a pharmaceutically acceptable excipient.

14. A polynucleotide that encodes the anti-hTREM2 antibody of any one of claims 1 to 12.

15. An expression vector comprising the polynucleotide of claim 14.

16. A host cell comprising the expression vector of claim 15.

17. A method of producing an anti-hTREM2 antibody that specifically binds to human TREM2 comprising culturing the host cell of claim 16 in a culture medium under conditions that allow expression of the anti-hTREM2 antibody; and recovering the anti-hTREM2 antibody from the culture medium or host cell.

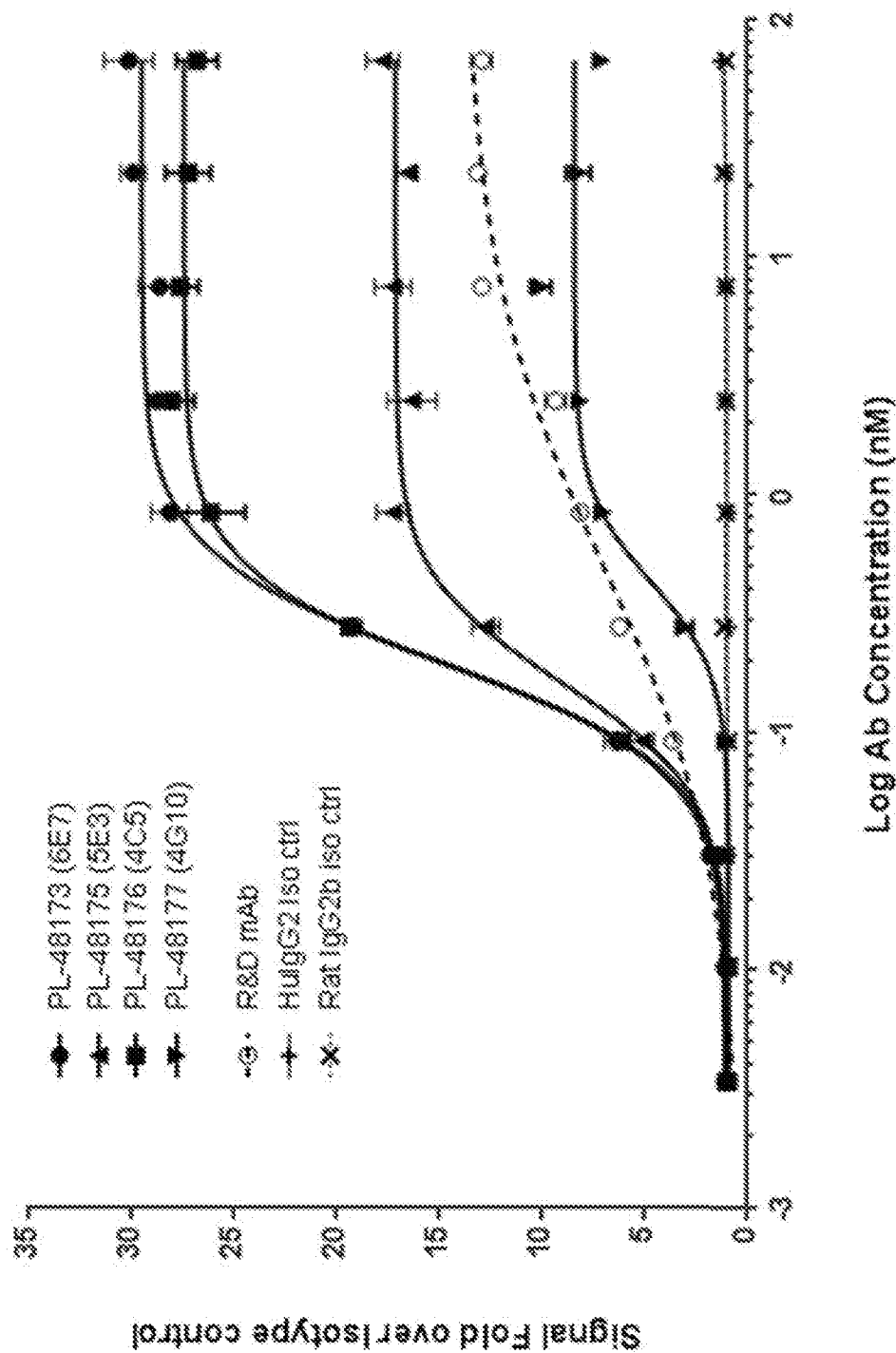


FIG. 1A

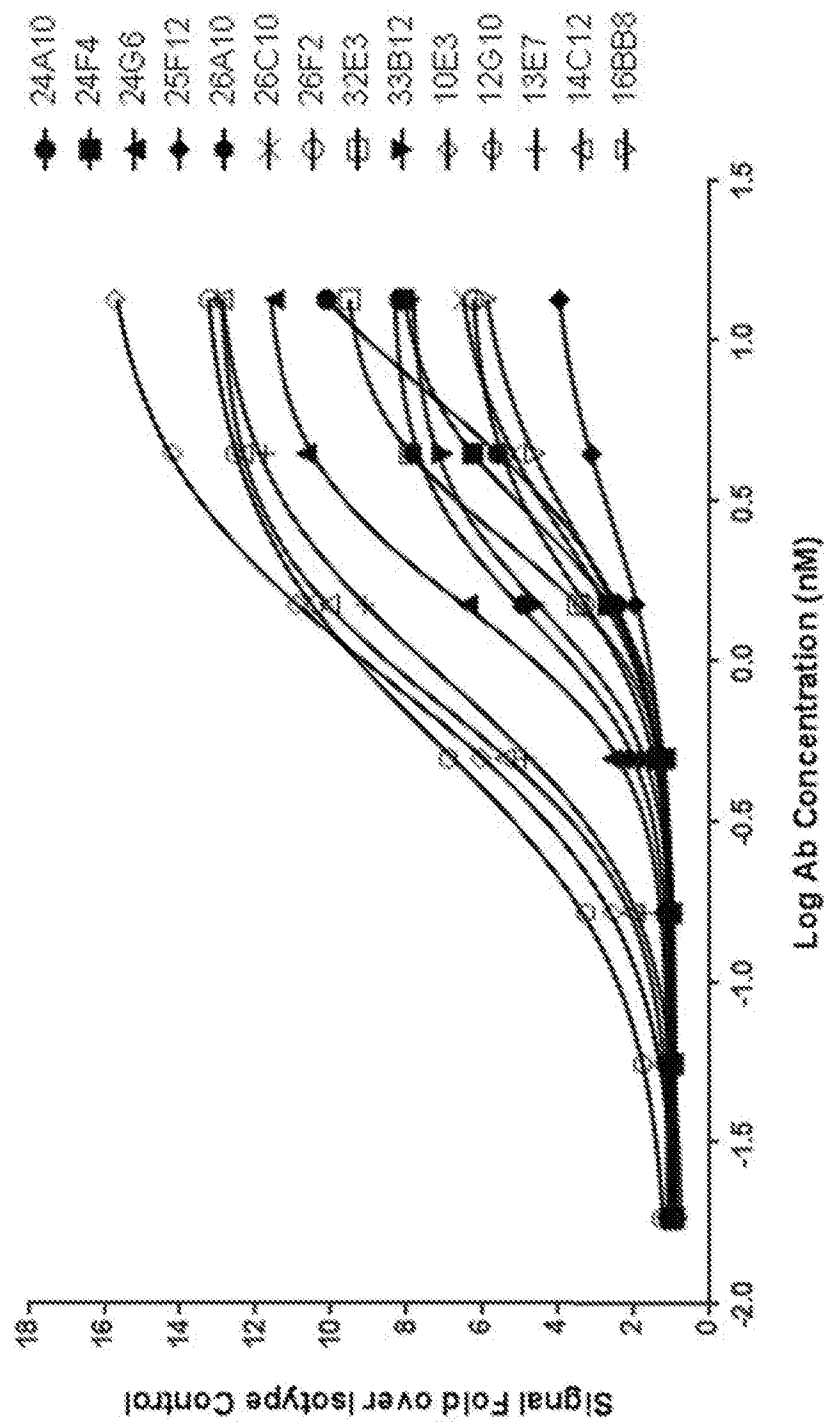


FIG. 1B

Ab ID.	Germline	SEQ ID NO:	K_FR1	K_CDR1	K_FR2	K_CDR2
	VK4 B3/JK5	64	DIVMTQSPDLSIAVSLGERATINC	KSS---QSVLYSSNNKNYLA	WYQQKPGQPPKLLIY	W-----ASTRES
24C12	VK4 B3/JK5	51	G.....	R.....	V...	
	VK4 B3/JK4	65	DIVMTQSPDLSIAVSLGERATINC	KSS---QSVLYSSNNKNYLA	WYQQKPGQPPKLLIY	W-----ASTRES
24G6	VK4 B3/JK4	52		HF..		
	VK4 B3/JK2	66	DIVMTQSPDLSIAVSLGERATINC	KSS---QSVLYSSNNKNYLA	WYQQKPGQPPKLLIY	W-----ASTRES
24A10	VK4 B3/JK2	53	T.	HN.....		
	VK3 L2/JK3	67	EIVMTQSPATLSVSPGERATLSC	RAS---QSVS-----SNLA	WYQQKPGQAPRLLIY	G-----ASTRAT
10E3	VK3 L2/JK3	54			.F.....	
13E7	VK3 L2/JK3	55			.F.....	
14C12	VK3 L2/JK1	68	EIVMTQSPATLSVSPGERATLSC	RAS---QSVS-----SNLA	WYQQKPGQAPRLLIY	G-----ASTRAT
25F12	VK3 L2/JK1	56	.K.....	N.....N...		
	VK3 A27/JK5	69	EIVLTQSPGTLSLSPGERATLSC	RAS---QSVSS-----SYLA	WYQQKPGQAPRLLIY	G-----ASSPAT
32E3	VK3 A27/JK5	57	.F.....	I.....N...		S.....
	VK3 A27/JK3	70	EIVLTQSPGTLSLSPGERATLSC	RAS---QSVSS-----SYLA	WYQQKPGQAPRLLIY	G-----ASSPAT
24F4	VK3 A27/JK3	58				
	VK1 L5/JK5	71	DIQMTQSPSSVSASVGDRTITC	RAS---QGIS-----SWLA	WYQQKPGKAPKLLIY	A-----ASSLQS
16B8	VK1 L5/JK5	59	V..	D.N.....		T
	VK1 L5/JK2	72	DIQMTQSPSSVSASVGDRTITC	RAS---QGIS-----SWLA	WYQQKPGKAPKLLIY	A-----ASSLQS
4C5	VK1 L5/JK2	60		N...		V
6E7	VK1 L5/JK2	61				N
	VK1 L1/JK3	73	DIQMTQSPSSLSASVGDRTITC	RAS---QGIS-----NYLA	WFQQKPGKAPKSLIY	A-----ASSLQS
5E3	VK1 L1/JK3	62				
	VK1 A30/JK1	74	DIQMTQSPSSLSASVGDRTITC	RAS---QGLR-----NDLG	WYQQKPGKAPKRLIY	A-----ASSLQS
4G10	VK1 A30/JK1	63			N.....	P.

FIG. 2A

Ab ID.	Germline	SEQ ID NO:	K_FR3	K_CDR3	K_FR4
	VK4 B3/JK5	64	GVPDFRFGSGSG--TDFTLTISLQAEDVAVYYC	QQYYS-----TPIT	FGQGRLEIK
24C12	VK4 B3/JK5	51	N.	I.....	
	VK4 B3/JK4	65	GVPDFRFGSGSG--TDFTLTISLQAEDVAVYYC	QQYYS-----TPLT	FGGGRKVEIK
24G6	VK4 B3/JK4	52	F...		
	VK4 B3/JK2	66	GVPDFRFGSGSG--TDFTLTISLQAEDVAVYYC	QQYYS-----TPYT	FGQGRKLEIK
24A10	VK4 B3/JK2	53		H.....CS	
	VK3 L2/JK3	67	GIPARFSGSG--TEFTLTISLQSEDFAVYYC	QQYNN-----WPFT	FGPGTKVDIK
10E3	VK3 L2/JK3	54	V.....F...	L.D.....P.	
13E7 14C12	VK3 L2/JK3	55	V.....	L.D.....P.	
	VK3 L2/JK1	68	GIPARFSGSG--TEFTLTISLQSEDFAVYYC	QQYNN-----WPWT	FGQGRKVEIK
25F12	VK3 L2/JK1	56		R.	
	VK3 A27/JK5	69	GIPDRFSGSG--TDFTLTISRLEPEDFVAVYYC	QQYGS-----SPIT	FGQGRLEIK
32E3	VK3 A27/JK5	57		..FD.....	..R....D..
	VK3 A27/JK3	70	GIPDRFSGSG--TDFTLTISRLEPEDFVAVYYC	QQYGS-----SPFT	FGPGTKVDIK
24F4	VK3 A27/JK3	58	L...	...DT.....	
	VK1 L5/JK5	71	GVPSRFGSGSG--TDFTLTISLQPEDFATYYC	QQANS-----FPIT	FGQGRLEIK
16B8	VK1 L5/JK5	59	S.	..S.....	
	VK1 L5/JK2	72	GVPSRFGSGSG--TDFTLTISLQPEDFATYYC	QQANS-----FPYT	FGQGRKLEIK
4C5	VK1 L5/JK2	60	...L.....	...D.....RN	
6E7	VK1 L5/JK2	61	F.	...D.....R.	
	VK1 L1/JK3	73	GVPSRFGSGSG--TDFTLTISLQPEDFATYYC	QQYNS-----YPFT	FGPGTKVDIK
5E3	VK1 L1/JK3	62	K.....	...ST.....	
	VK1 A30/JK1	74	GVPSRFGSGSG--TEFTLTISLQPEDFATYYC	LQHNS-----YPWT	FGQGRKVEIK
4G10	VK1 A30/JK1	63	P.....	T	

FIG. 2B

Ab ID.	Germline	SEQ ID NO:	L_FR1	L_CDR1	L_FR2	L_CDR2
	VL5 5c/JL2	75	QAVLTQP-ASLSASPGASASLTC	TLPS-GINVGT-----YRIY	WYQQKPGSPFPQYILR	YKS-----DSDKQQGS
12G10	VL5 5c/JL2	46	...P....S.....VL.....			
	VL3 3r/JL2	76	SYELTQP-PSVSVSPGGTASITC	SGD---KLGD-----KYAC	WYQQKPGQSPVLVIY	Q-----DSKRPS
26A10	VL3 3r/JL2	47		V.		
26C10	VL3 3r/JL2	48	.F.....	V.	M....	T....
26F2	VL3 3r/JL2	49		V.	F	
33B12	VL3 3r/JL2	50		V.		

FIG. 3A

Ab ID.	Germline	SEQ ID NO:	L_FR3	L_CDR3	L_FR4
	VL5 5c/JL2	75	GVFSRFSGSKDASANAGILLISGLQSEDEADYYC	MIWHS-----SASVV	FGGGTKLTIVL
12G10	VL5 5c/JL2	46		...Y.....-SA..	
	VL3 3r/JL2	76	GIPERFSGNSG--NTATLTISGTQAMDEADYYC	QAWDS-----STAVV	FGGGTKLTIVL
26A10	VL3 3r/JL2	47		-NT..	
26C10	VL3 3r/JL2	48		-ST..	
26F2	VL3 3r/JL2	49		-ST..	
33B12	VL3 3r/JL2	50		-ST..	

FIG. 3B

Ab ID.	Germline	SEQ ID NO:	H_FR1	H_CDR1	H_FR2	H_CDR2
	VH3 3-23/D3 3-16 RF2/JH4	127	EVQLLES-GGGLVQPGGSLRLSCAASG-FTFS	S-----YAMS	WVRQAPGKGLEWVS	AISSG----GGSTYYADSVKG
12G10	VH3 3-23/D3 3-16 RF2/JH4	110				..G.G....V...C.....
24C12	VH3 3-23/D3 3-16 RF2/JH4	110				..G.G....V...C.....
	VH3 3-48/D7 7-27 RF1/JH6	128	EVQLVES-GGGLVQPGGSLRLSCAASG-FTFS	S-----YSMN	WVRQAPGKGLEWVS	YISSS----SSTIYYADSVKG
26A10	VH3 3-48/D7 7-27 RF1/JH6	111	A...R.....R....	FG.S		F.....
26C10	VH3 3-48/D7 7-27 RF1/JH6	112	A.....	FG.S		F.....
26F2	VH3 3-48/D7 7-27 RF1/JH6	113	A.....	FG.S	I.	F.....
33B12	VH3 3-48/D7 7-27 RF1/JH6	114	A.....	FG.S		..K....F.....
	VH3 3-23/D2 2-21 RF2/JH4	129	EVQLLES-GGGLVQPGGSLRLSCAASG-FTFS	S-----YAMS	WVRQAPGKGLEWVS	AISSG----GGSTYYADSVKG
24G6	VH3 3-23/D2 2-21 RF2/JH4	115				
	VH3 3-23/D1 1-1 RF1/JH1	130	EVQLLES-GGGLVQPGGSLRLSCAASG-FTFS	S-----YAMS	WVRQAPGKGLEWVS	AISSG----GGSTYYADSVKG
24A10	VH3 3-23/D1 1-1 RF1/JH1	116	...V.....	N.....		
	VH5 5-51/D1 1-1 RF1/JH4	131	EVQLVQS-GAEVKKPGESLKISCKSGG-YSFT	S-----YWIG	WVRQMPGKGLEMMG	IIYPG----DSDTRYSPSFQG
10E3	VH5 5-51/D1 1-1 RF1/JH4	117	M.....	N.....		
13E7	VH5 5-51/D1 1-1 RF1/JH4	118	M.....			
14C12						
	VH4 4-34/D1 1-1 RF3/JH3	132	QVQLQQW-GAGLLKPSSETLSLTCAVYG-GSFS	G-----YVWS	WIRQPPGKGLEWIG	EINH-----SGSTNYNPSLKS
25F12	VH4 4-34/D1 1-1 RF3/JH3	119		S.....		N.....
	VH5 5-51/D5 5-12 RF1/JH3	133	EVQLVQS-GAEVKKPGESLKISCKSGG-YSFT	S-----YWIG	WVRQMPGKGLEMMG	IIYPG----DSDTRYSPSFQG
32E3	VH5 5-51/D5 5-12 RF1/JH3	120				
	VH5 5-51/D5 5-12 RF1/JH5	134	EVQLVQS-GAEVKKPGESLKISCKSGG-YSFT	S-----YWIG	WVRQMPGKGLEMMG	IIYPG----DSDTRYSPSFQG
24F4	VH5 5-51/D5 5-12 RF1/JH5	121	T..			
	VH1 1-18/D1 1-26 RF3/JH4	135	QVQLVQS-GAEVKKPGASVKVSKASG-YTFT	S-----YGIS	WVRQAPGQGLEMMG	WISAY----NGNTNYAQKLQG
16B8	VH1 1-18/D1 1-26 RF3/JH4	122		N.....		
	VH5 5-51/D1 1-26 RF3/JH4	136	EVQLVQS-GAEVKKPGESLKISCKSGG-YSFT	S-----YWIG	WVRQMPGKGLEMMG	IIYPG----DSDTRYSPSFQG
4C5	VH5 5-51/D1 1-26 RF3/JH4	123	H...	N.....A		
6E7	VH5 5-51/D1 1-26 RF3/JH4	124		A		
	VH1 1-02/D4 4-17 RF2/JH6	137	QVQLVQS-GAEVKKPGASVKVSKASG-YTFT	G-----YVMH	WVRQAPGQGLEMMG	WINPN----SGGTNYAQKFGG
5E3	VH1 1-02/D4 4-17 RF2/JH6	125		I.		...Y.....TS.....
	VH5 5-51/D5 5-12 RF1/JH6	138	EVQLVQS-GAEVKKPGESLKISCKSGG-YSFT	S-----YWIG	WVRQMPGKGLEMMG	IIYPG----DSDTRYSPSFQG
4G10	VH5 5-51/D5 5-12 RF1/JH6	126	P	A		

FIG. 4A

Ab ID.	Germline	SEQ ID NO:	H_FR3	H_CDR3	H_FR4
	VH3 3-23/D3 3-16 RF2/JH4	127	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK	YDYVWGS-----YRYTYFDY	WGQGTLLVTVSS
12G10	VH3 3-23/D3 3-16 RF2/JH4	110		F.IA.A--.....--GSH...	
24C12	VH3 3-23/D3 3-16 RF2/JH4	110		F.IA.A--.....--GSH...	
	VH3 3-48/D7 7-27 RF1/JH6	128	RFTISRDNAKNSLYLQMNSLRDEDTAVYYCAK	LTGYYY-----YYGMDV	WGQGTLLVTVSS
26A10	VH3 3-48/D7 7-27 RF1/JH6	111	F.....	EG.LTMVRG.....VSS..L..	
26C10	VH3 3-48/D7 7-27 RF1/JH6	112	F.....F.V.	EG. ITMVRG.....VSS.....	
26F2	VH3 3-48/D7 7-27 RF1/JH6	113	F.....F...	EG. ITMVRG.....VSS.....	
33B12	VH3 3-48/D7 7-27 RF1/JH6	114	F.....	EG.LTMVRG.....VSS..L..	
	VH3 3-23/D2 2-21 RF2/JH4	129	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK	AYCGGDC-----YSYFDY	WGQGTLLVTVSS
24C6	VH3 3-23/D2 2-21 RF2/JH4	115		..TPM-----AF...	
	VH3 3-23/D1 1-1 RF1/JH1	130	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK	GTGTGTA-----EYFQH	WGQGTLLVTVSS
24A10	VH3 3-23/D1 1-1 RF1/JH1	116		.GWE-----LFY	
	VH5 5-51/D1 1-1 RF1/JH4	131	QVTISADKSI STAYLQWSSSLKASDTAMYYCAK	GTGTG-----YFDY	WGQGTLLVTVSS
10E3	VH5 5-51/D1 1-1 RF1/JH4	117	F...	RRQ.IW.....GDAL.I	
13E7	VH5 5-51/D1 1-1 RF1/JH4	118	F...	RRQ.IW.....GDAL.F	
14C12					
	VH4 4-34/D1 1-1 RF3/JH3	132	RVTISVDTSKNQFSLKSLSSVTAADTAVYYCAK	YNWND-----DAFDI	WGQGTLLVTVSS
25F12	VH4 4-34/D1 1-1 RF3/JH3	119		EGYY.ILT.....GYH.....	.D.....F.
	VH5 5-51/D5 5-12 RF1/JH3	133	QVTISADKSI STAYLQWSSSLKASDTAMYYCAK	VDIVAT-----IDAFDI	WGQGTLLVTVSS
32E3	VH5 5-51/D5 5-12 RF1/JH3	120	T.....I.....	H..IPAA.....PG....	
	VH5 5-51/D5 5-12 RF1/JH5	134	QVTISADKSI STAYLQWSSSLKASDTAMYYCAK	VDIVAT-----INWFDP	WGQGTLLVTVSS
24F4	VH5 5-51/D5 5-12 RF1/JH5	121	V...S.....I...T.	QA.AV.G.....LGG...	
	VH1 1-18/D1 1-26 RF3/JH4	135	RVTMTTDTSTAYMELSLRSDDTAVYYCAK	YSGSY-----YYFDY	WGQGTLLVTVSS
16B8	VH1 1-18/D1 1-26 RF3/JH4	122	V.....	RGY.....GS...	
	VH5 5-51/D1 1-26 RF3/JH4	136	QVTISADKSI STAYLQWSSSLKASDTAMYYCAK	YSGSY-----YYFDY	WGQGTLLVTVSS
4C5	VH5 5-51/D1 1-26 RF3/JH4	123	V.F...	QRTF.YD.....SSG....	
6E7	VH5 5-51/D1 1-26 RF3/JH4	124	F...	QRTF.YD.....SSD....	
	VH1 1-02/D4 4-17 RF2/JH6	137	RVTMTTDTSTAYMELSLRSDDTAVYYCAK	DYGDYYY-----YYGMDV	WGQGTLLVTVSS
5E3	VH1 1-02/D4 4-17 RF2/JH6	125	S.....	.G.YLA-----L..T..	
	VH5 5-51/D5 5-12 RF1/JH6	138	QVTISADKSI STAYLQWSSSLKASDTAMYYCAK	VDIVATY-----YYGMDV	WGQGTLLVTVSS
4G10	VH5 5-51/D5 5-12 RF1/JH6	126	F.K.....F...	QG.EV.G-----TG.L..	

FIG. 4B

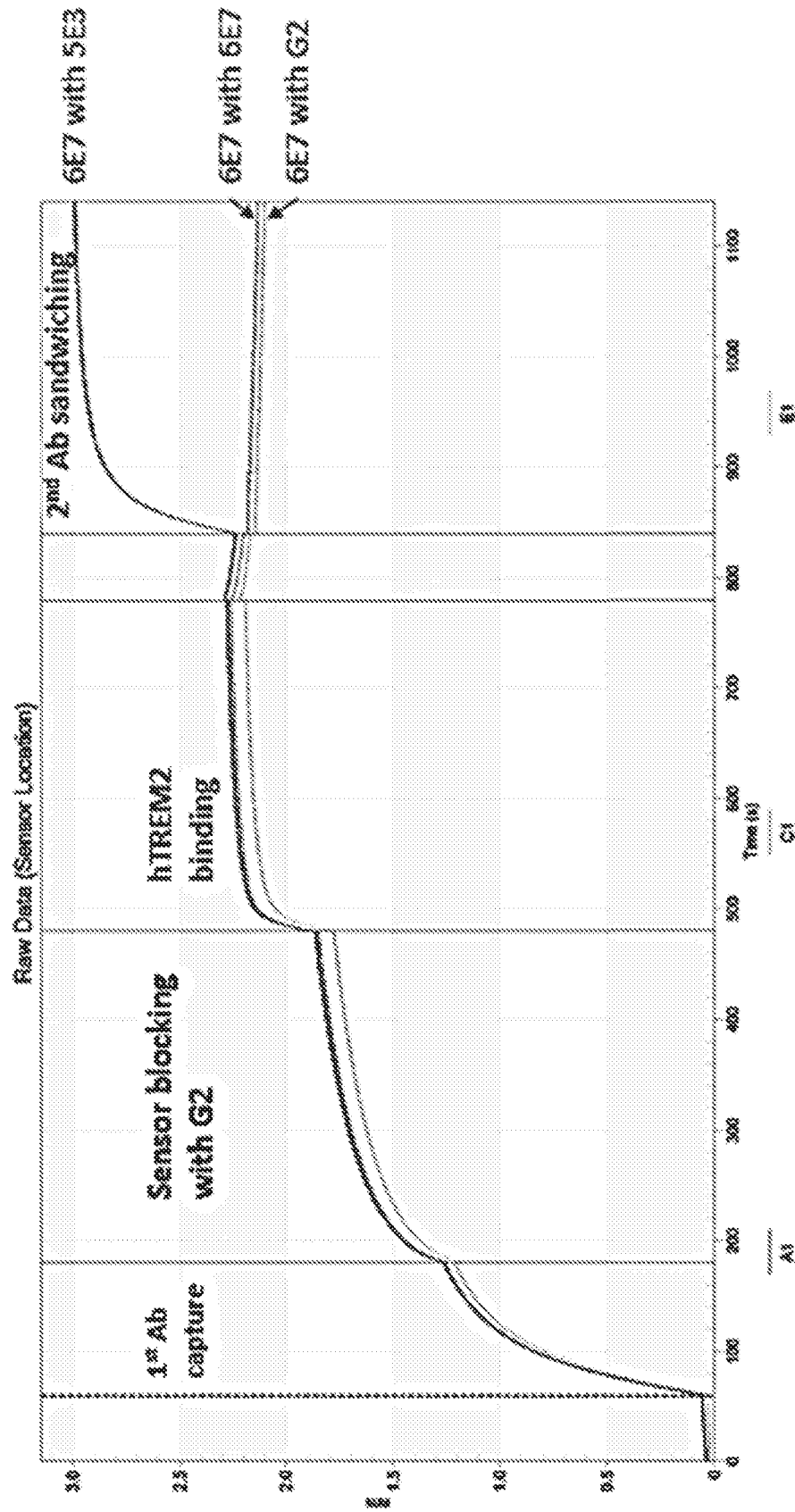


FIG. 5

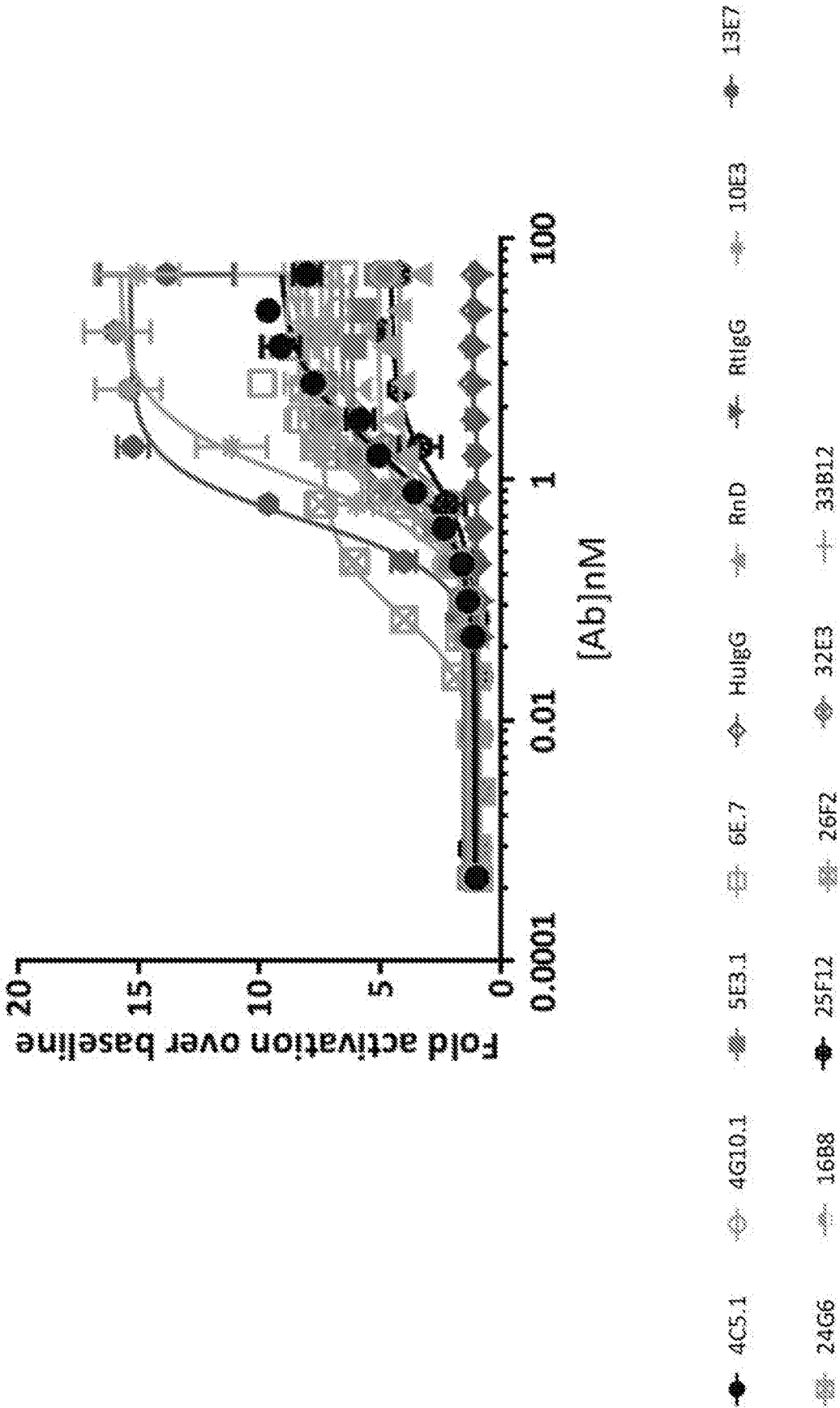


FIG. 6

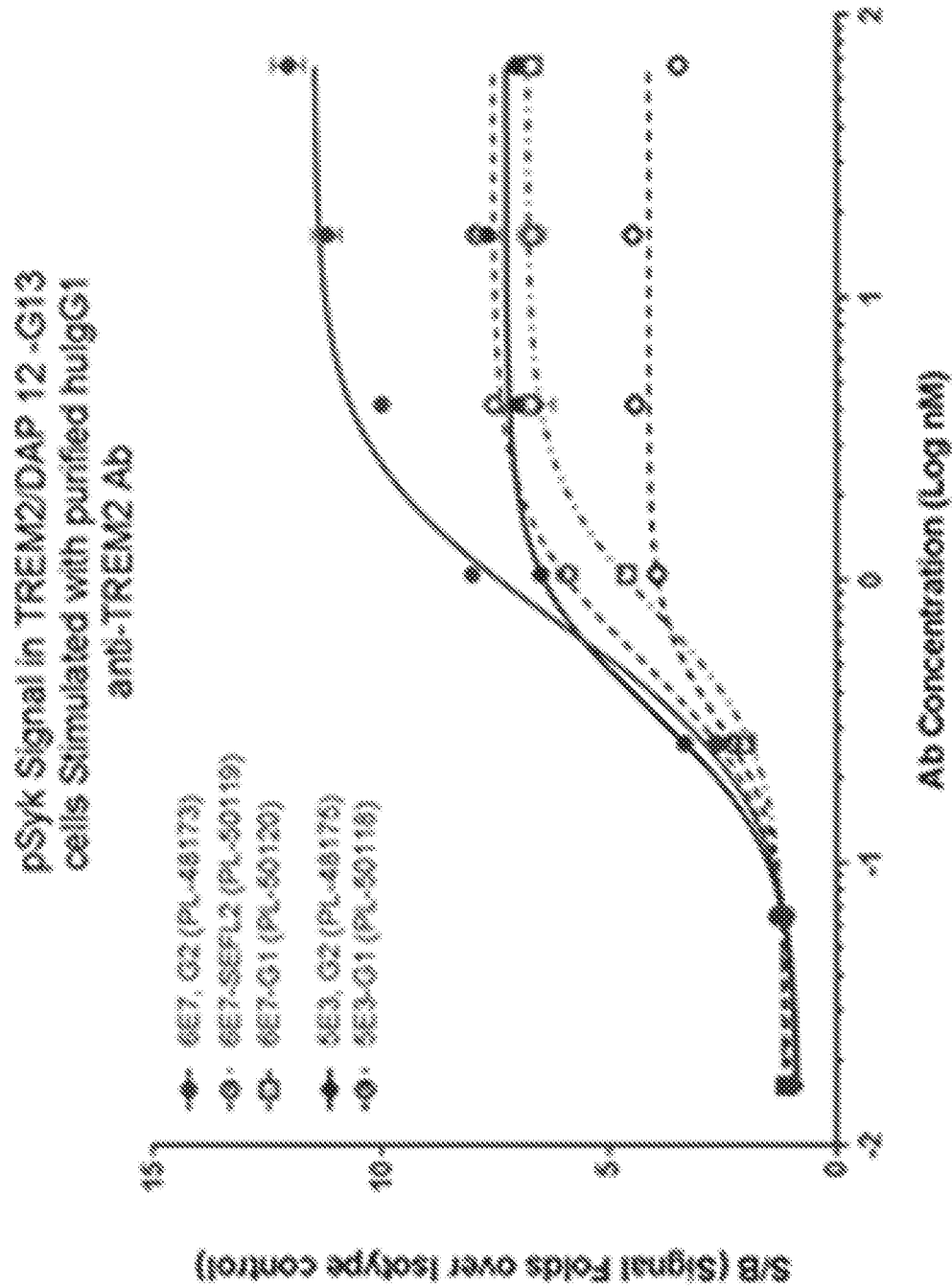


FIG. 7

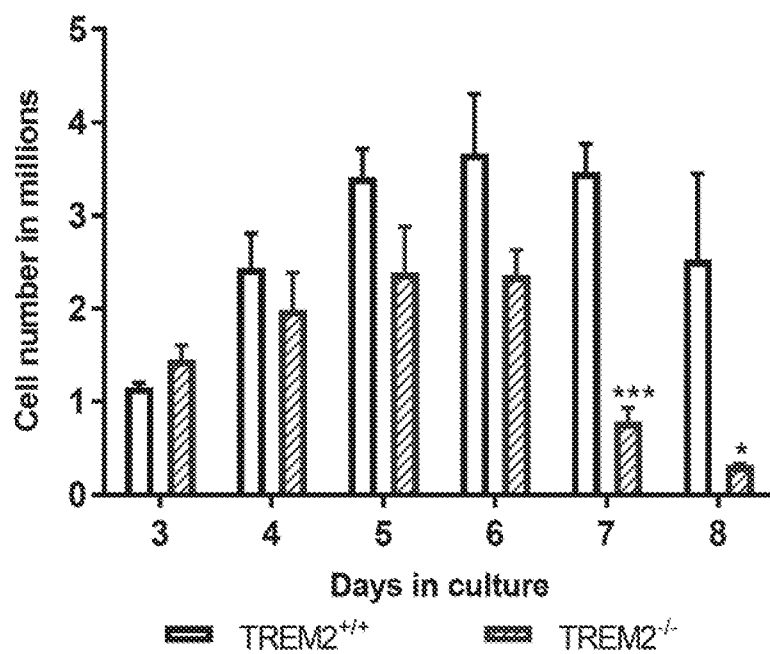


FIG. 8A

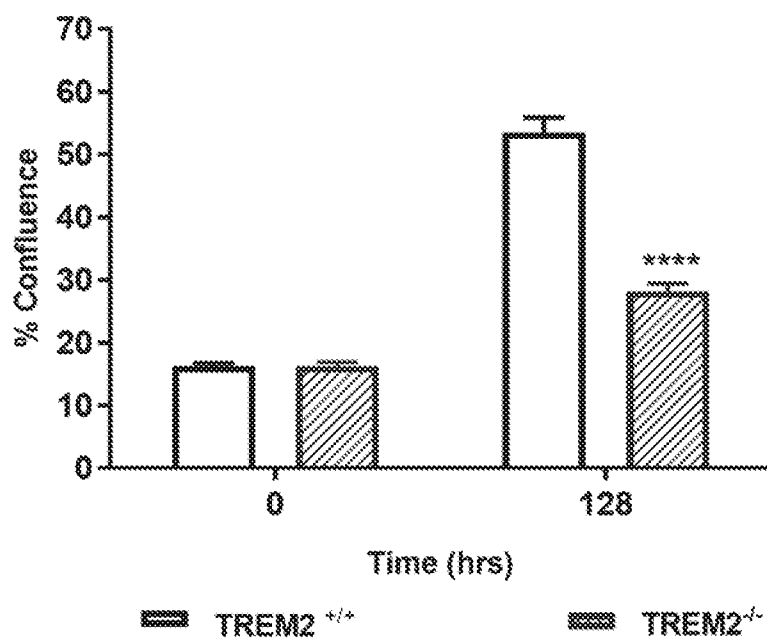


FIG. 8B

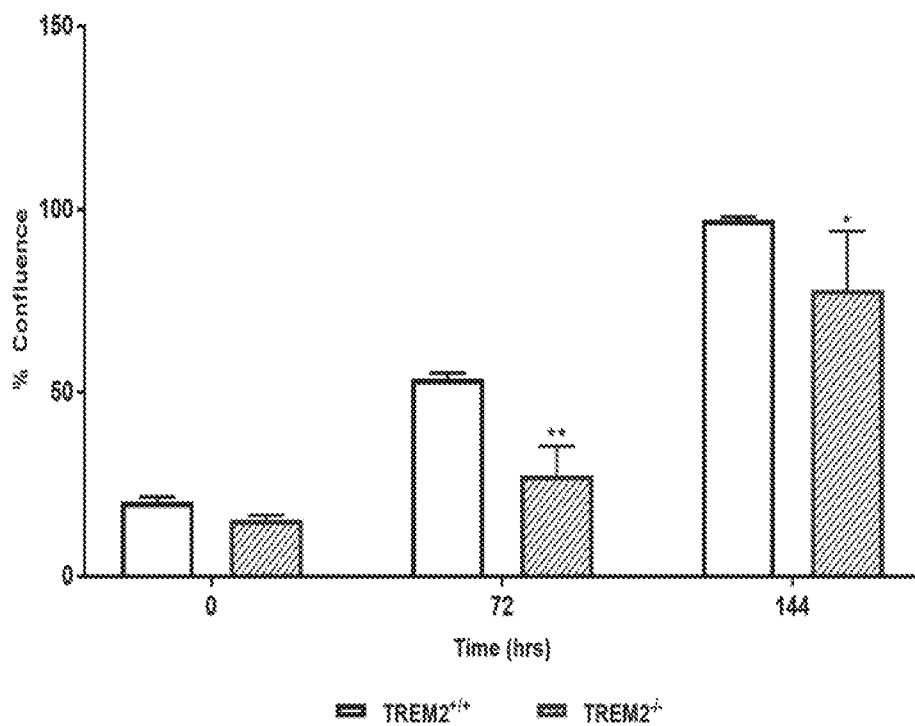


FIG. 8C

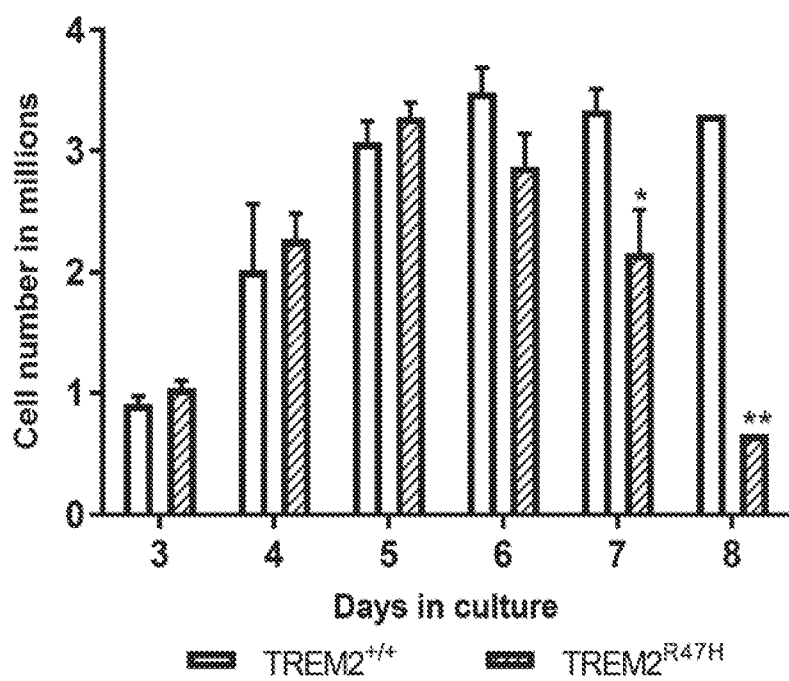


FIG. 8D

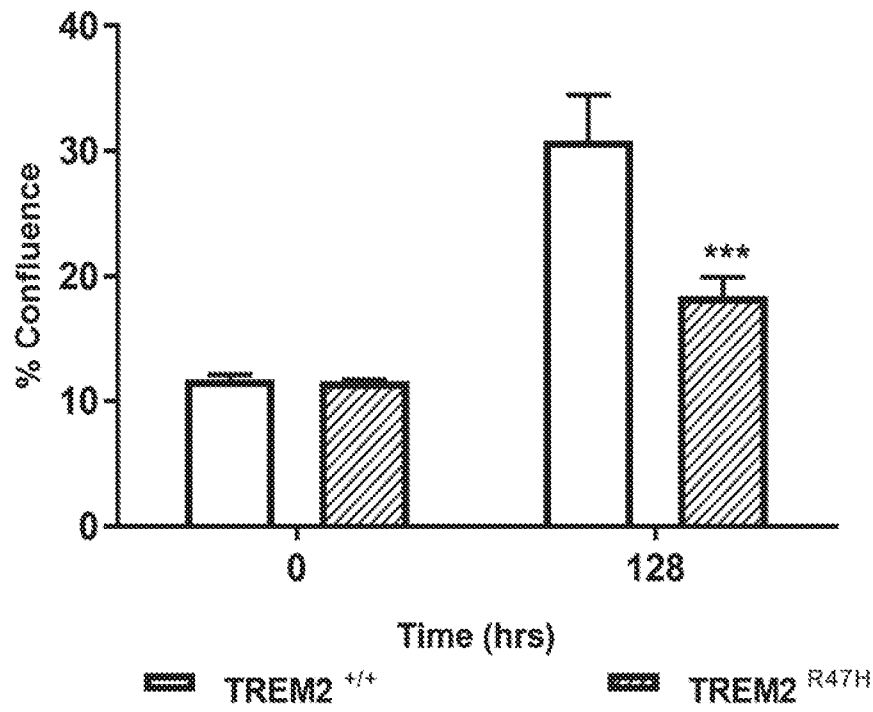


FIG. 8E

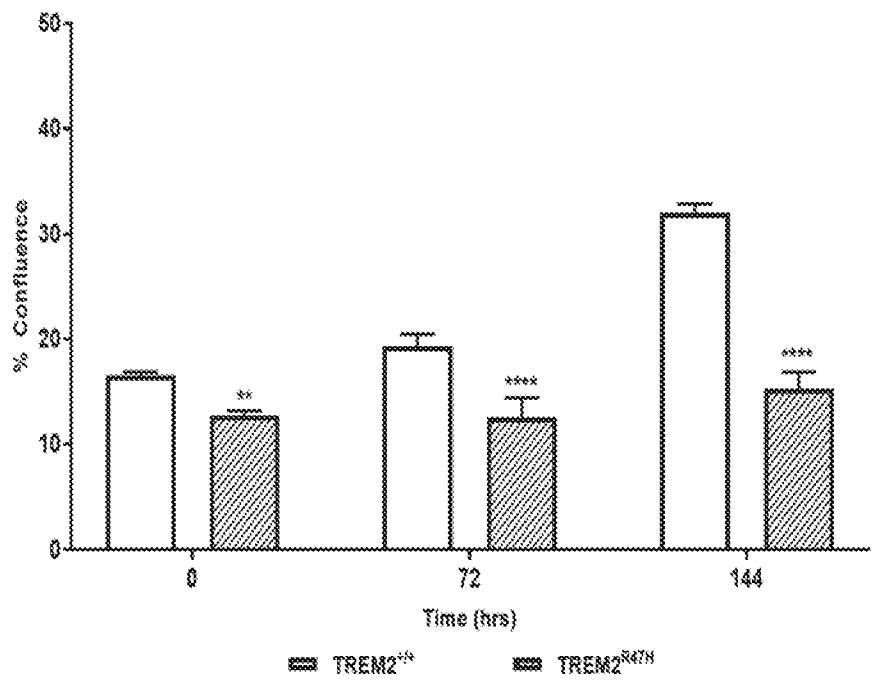
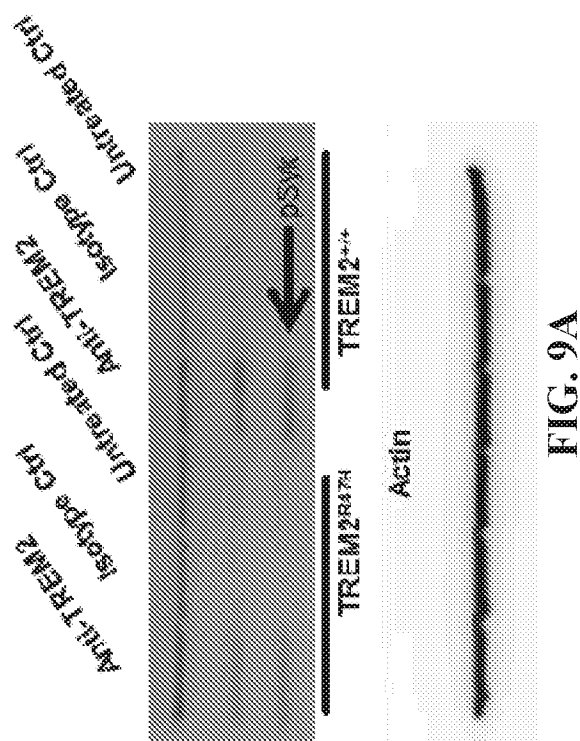


FIG. 8F



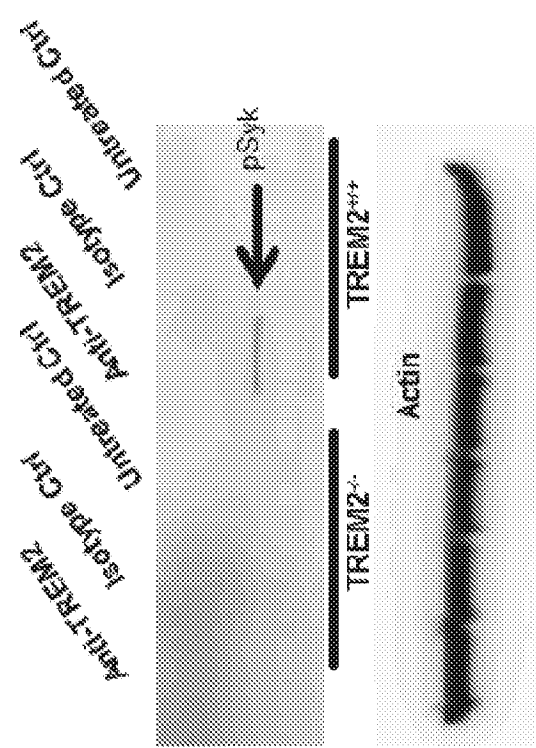


FIG. 9B

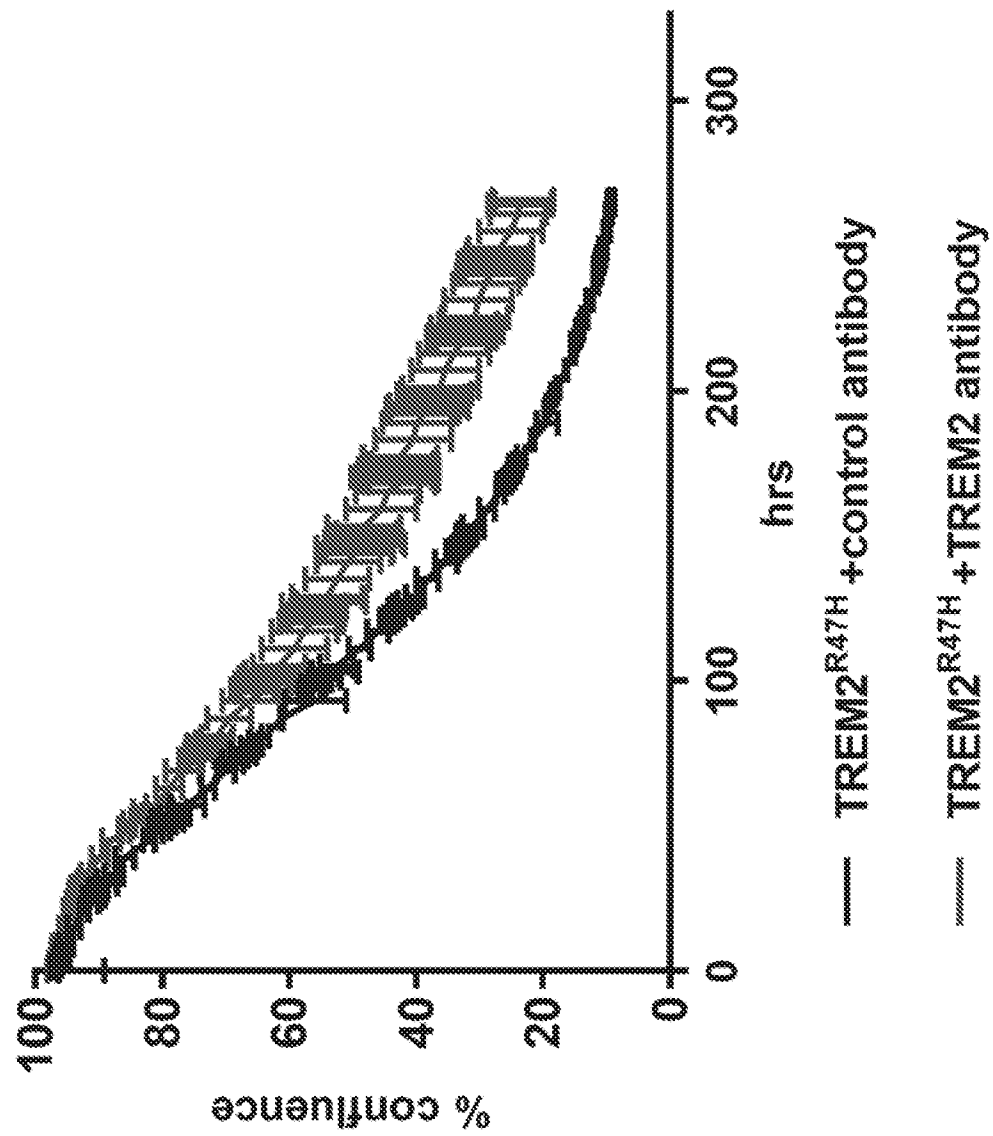


FIG. 10A

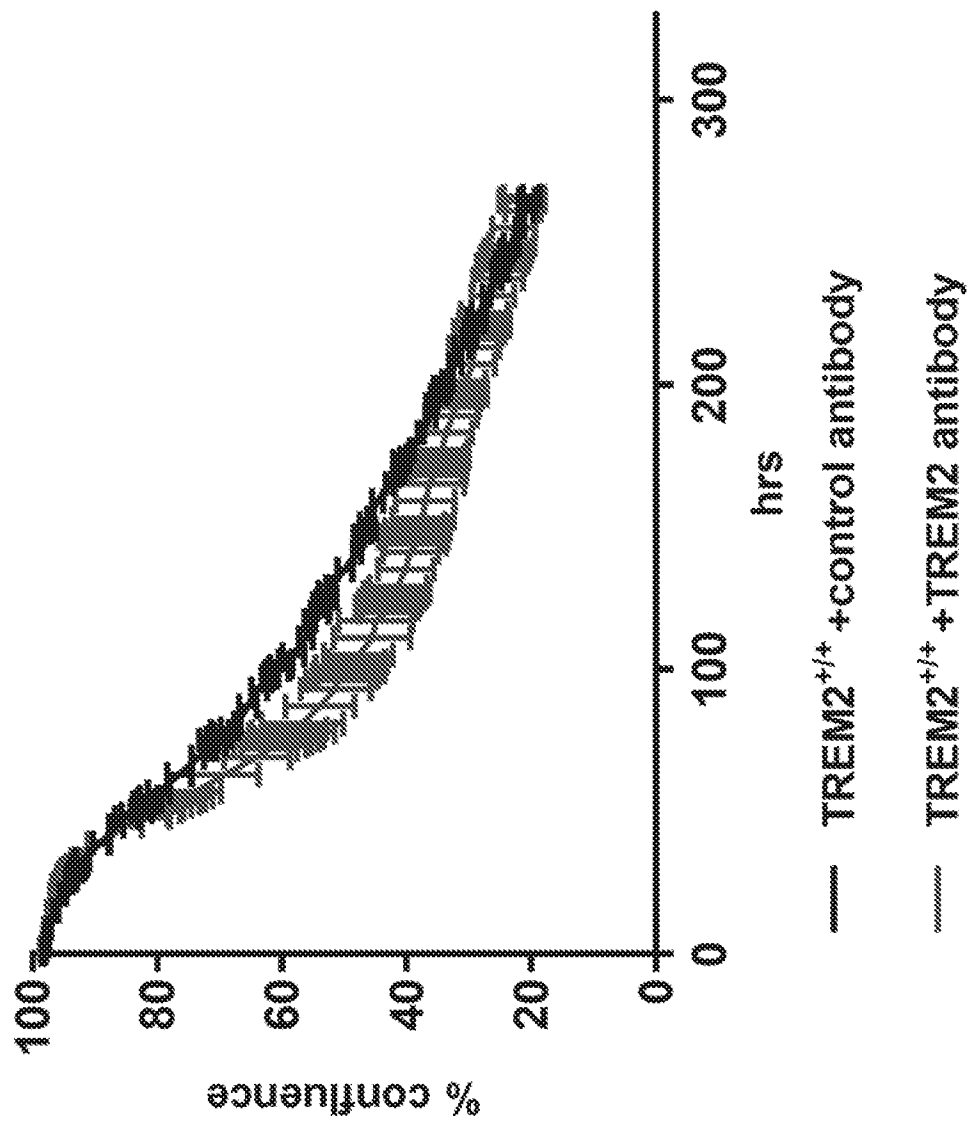
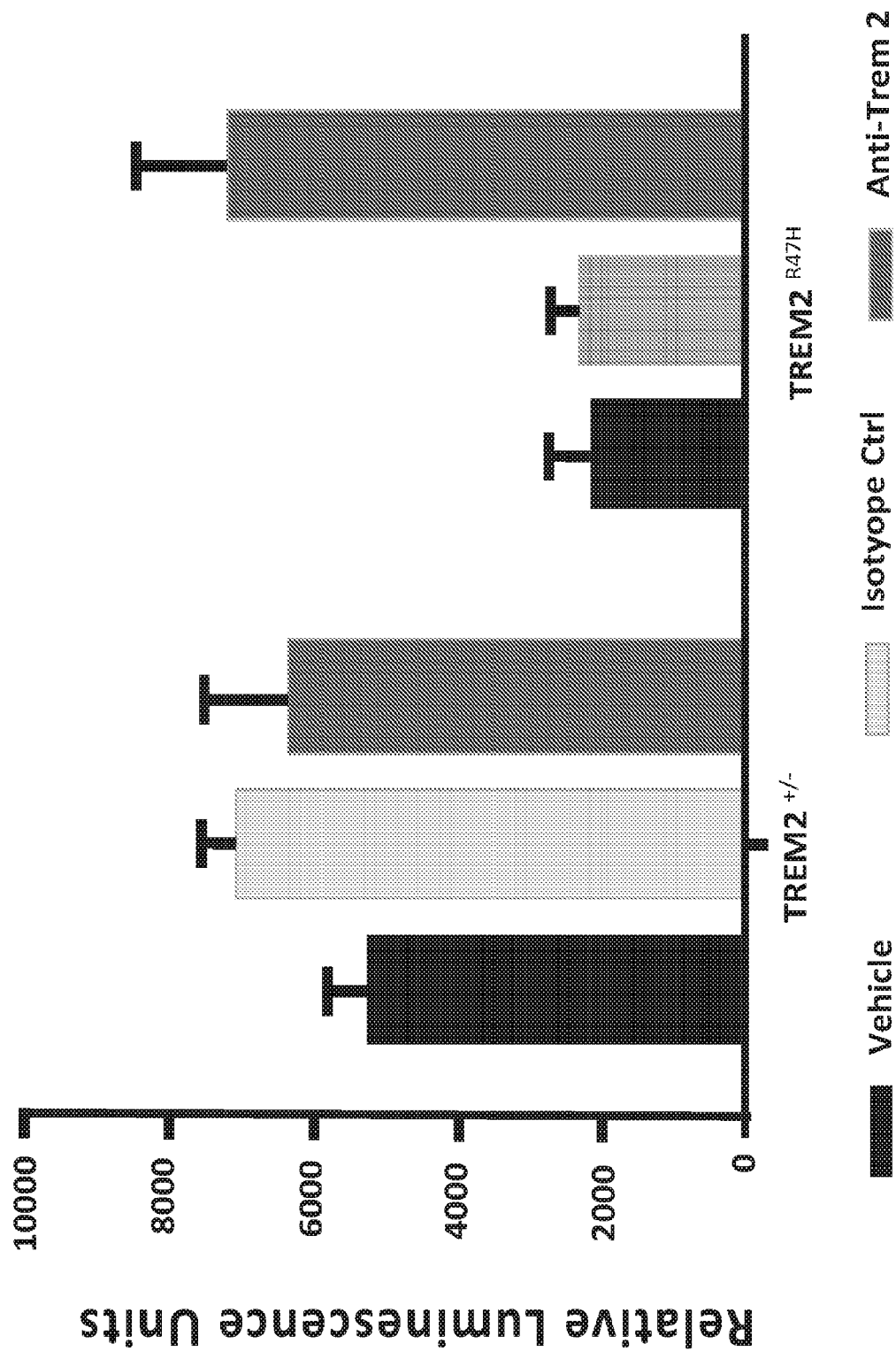


FIG. 10B

FIG. 10C



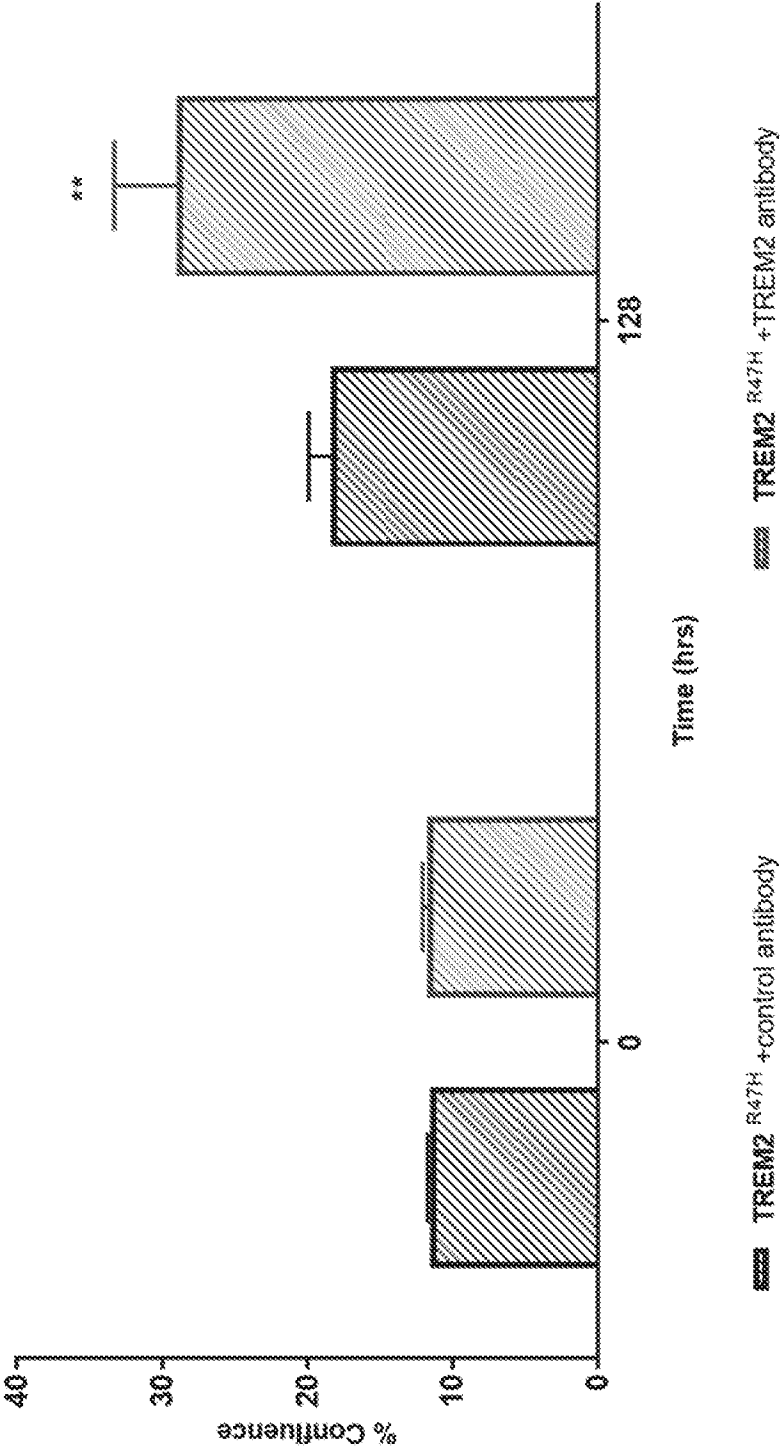


FIG. 10D

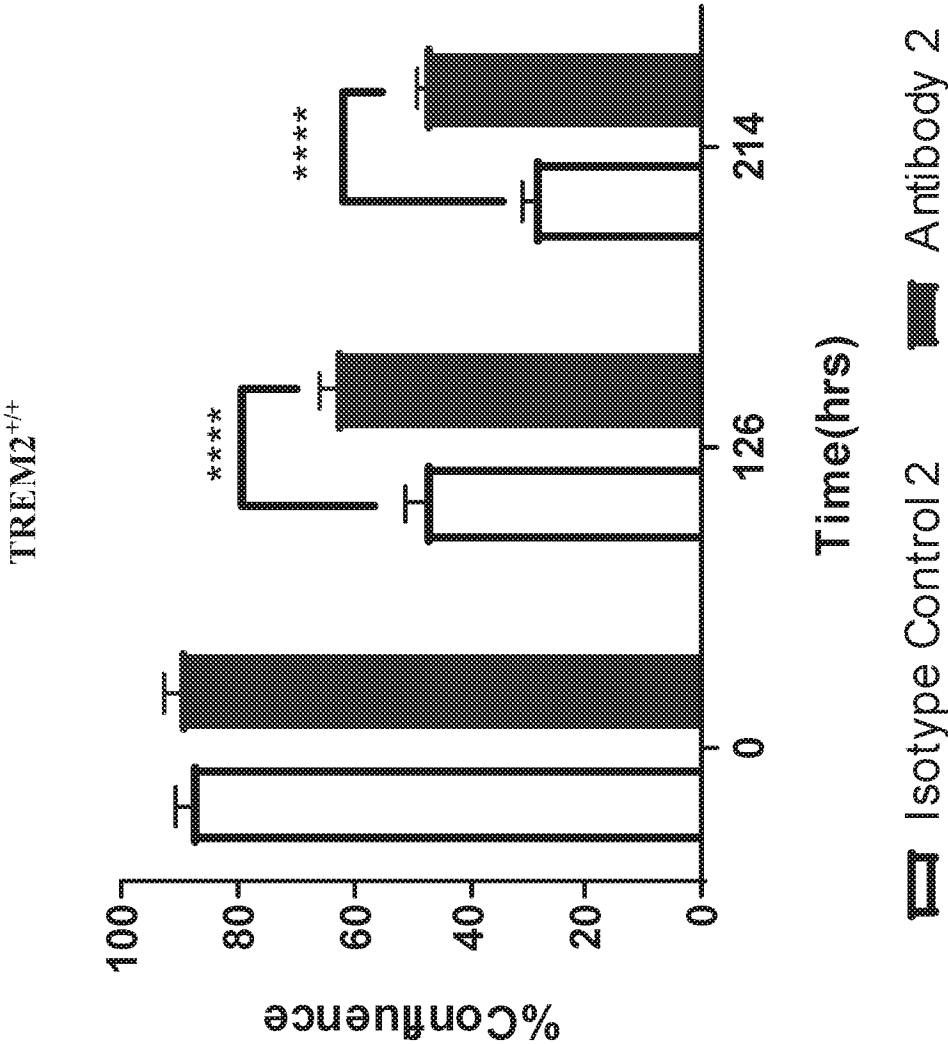


FIG. 10E

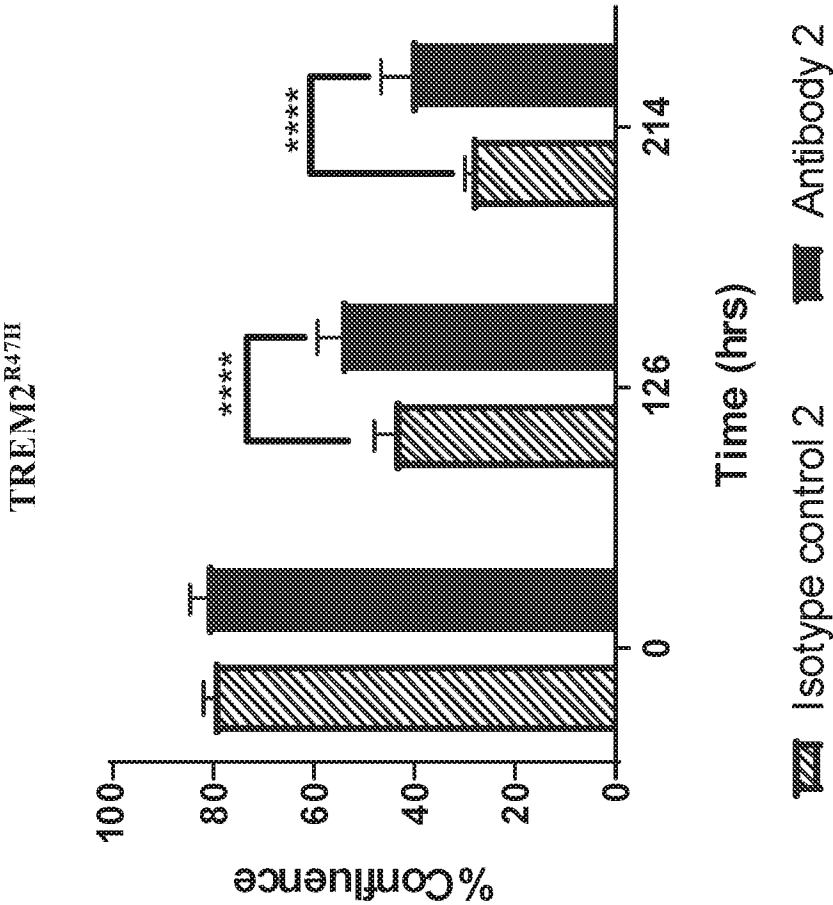


FIG. 10F

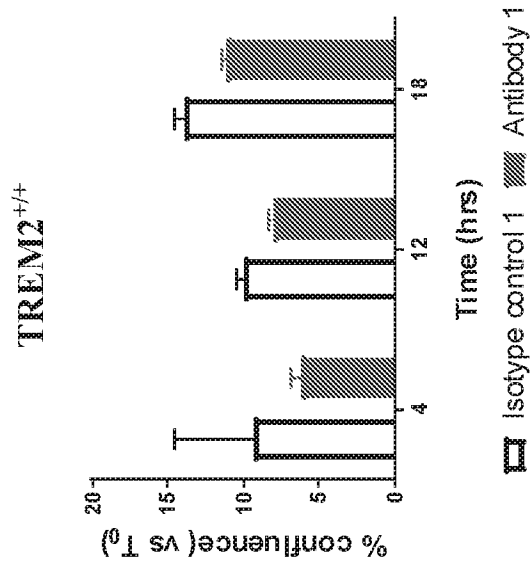


FIG. 11A

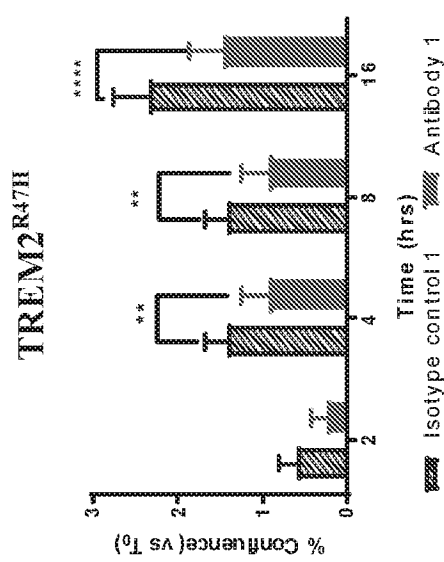


FIG. 11B

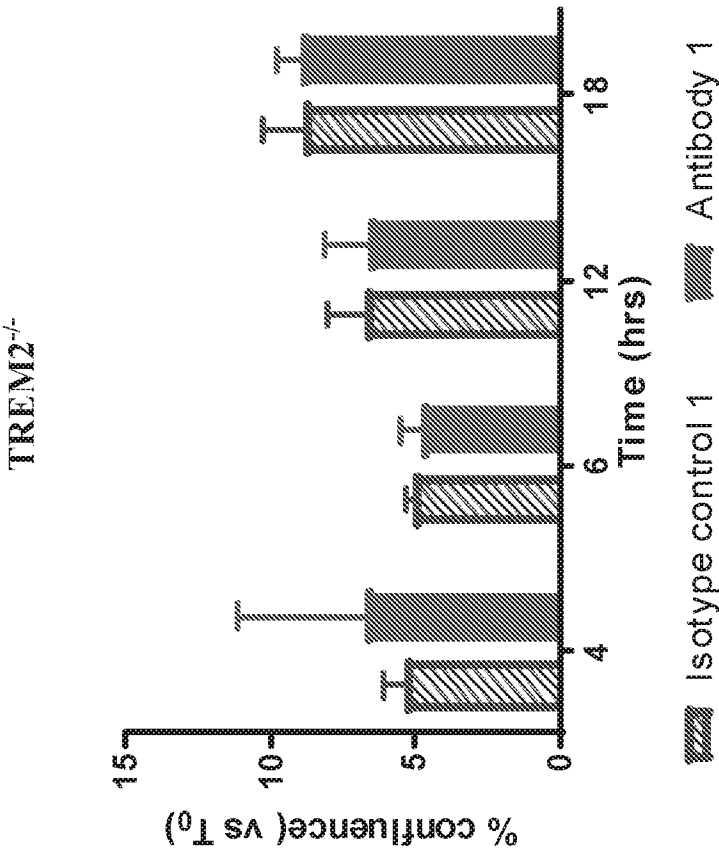


FIG. 11C

TREM2^{+/+}

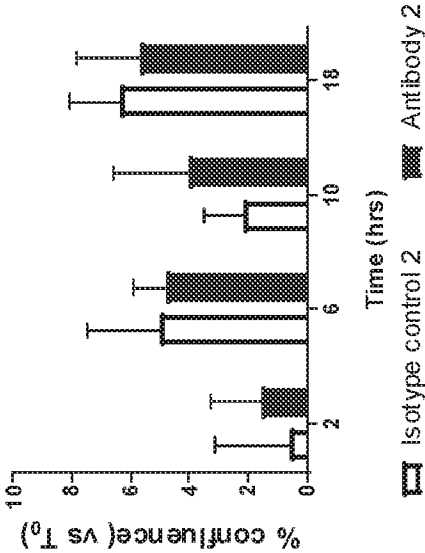


FIG. 11D

TREM2^{R47H}

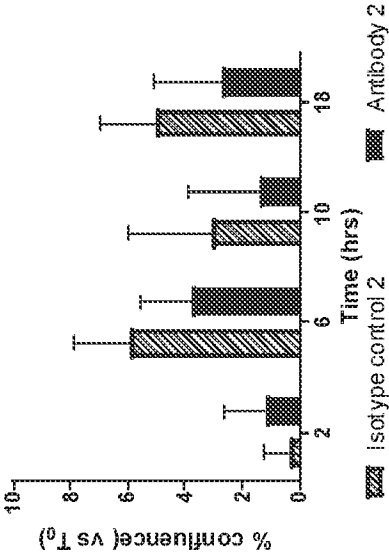


FIG. 11E

FIG. 12A

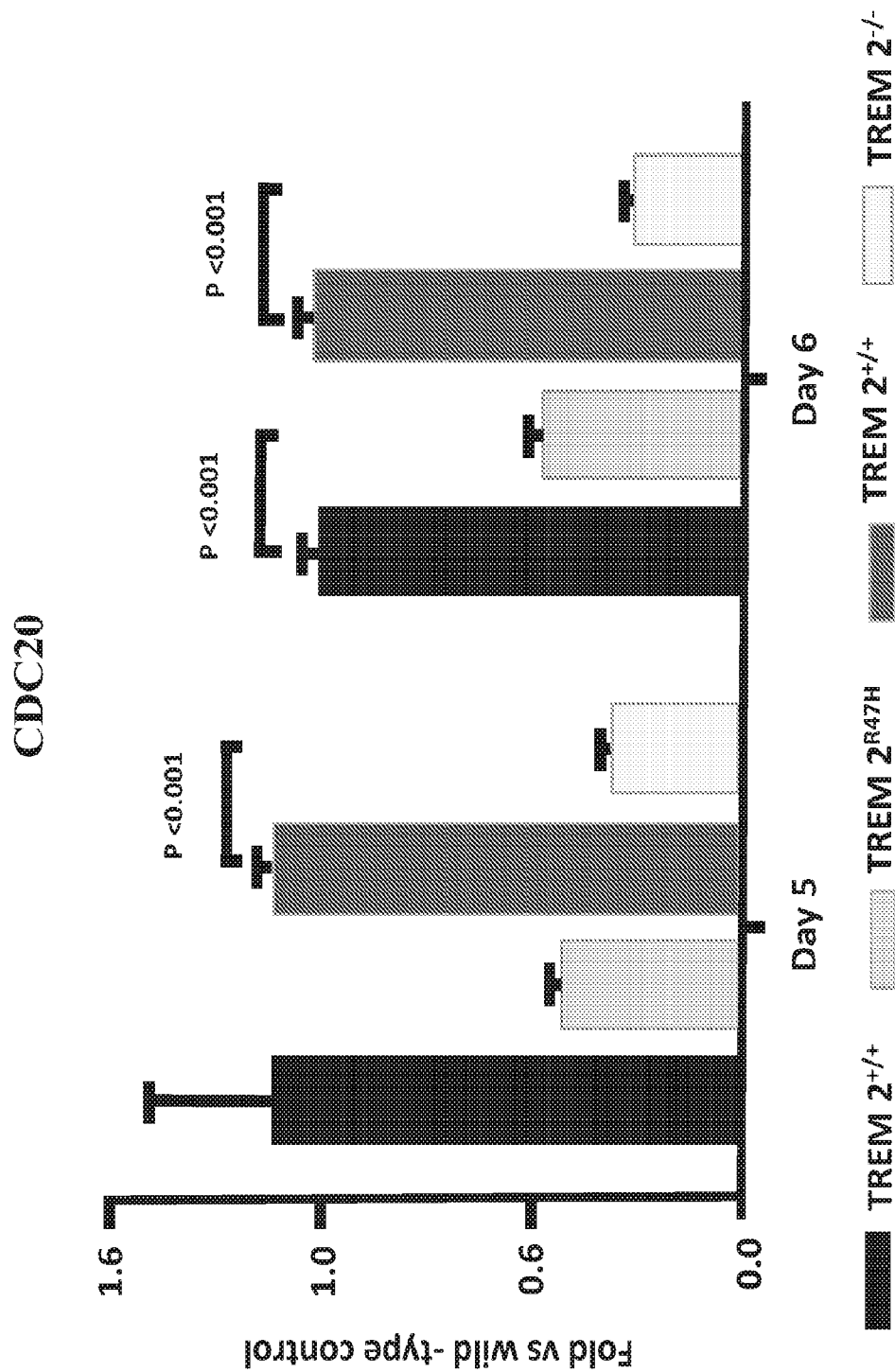


FIG. 12B

PKB

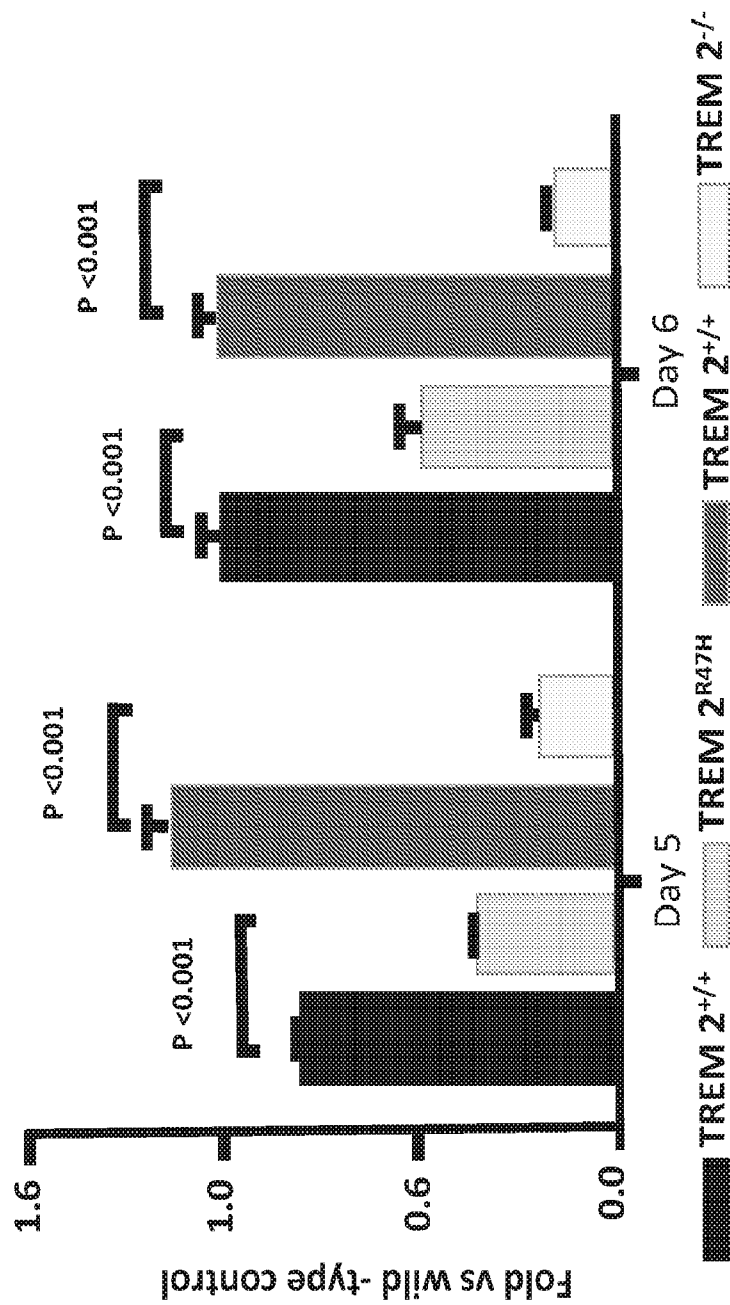


FIG. 12C

NDC80

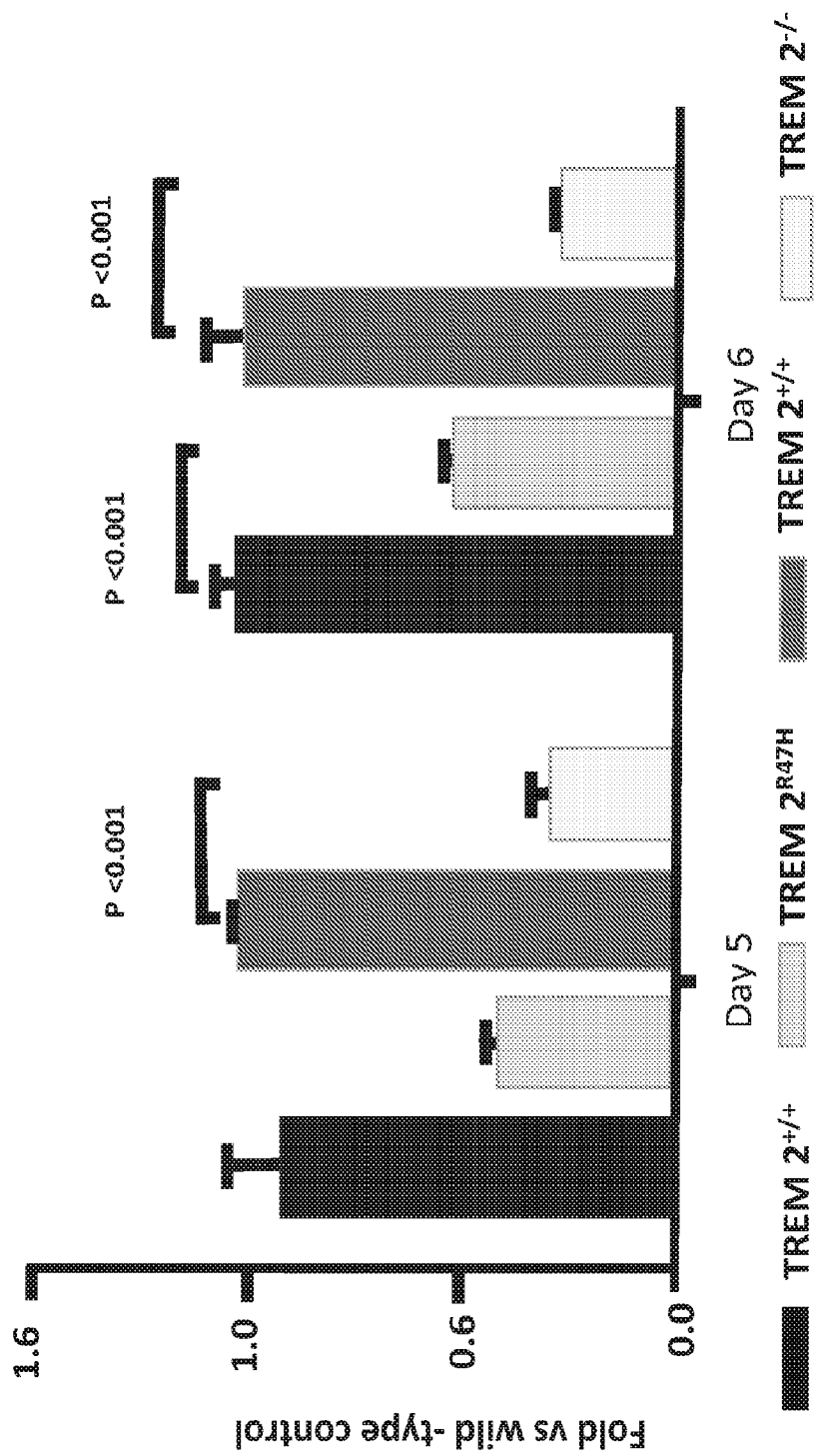
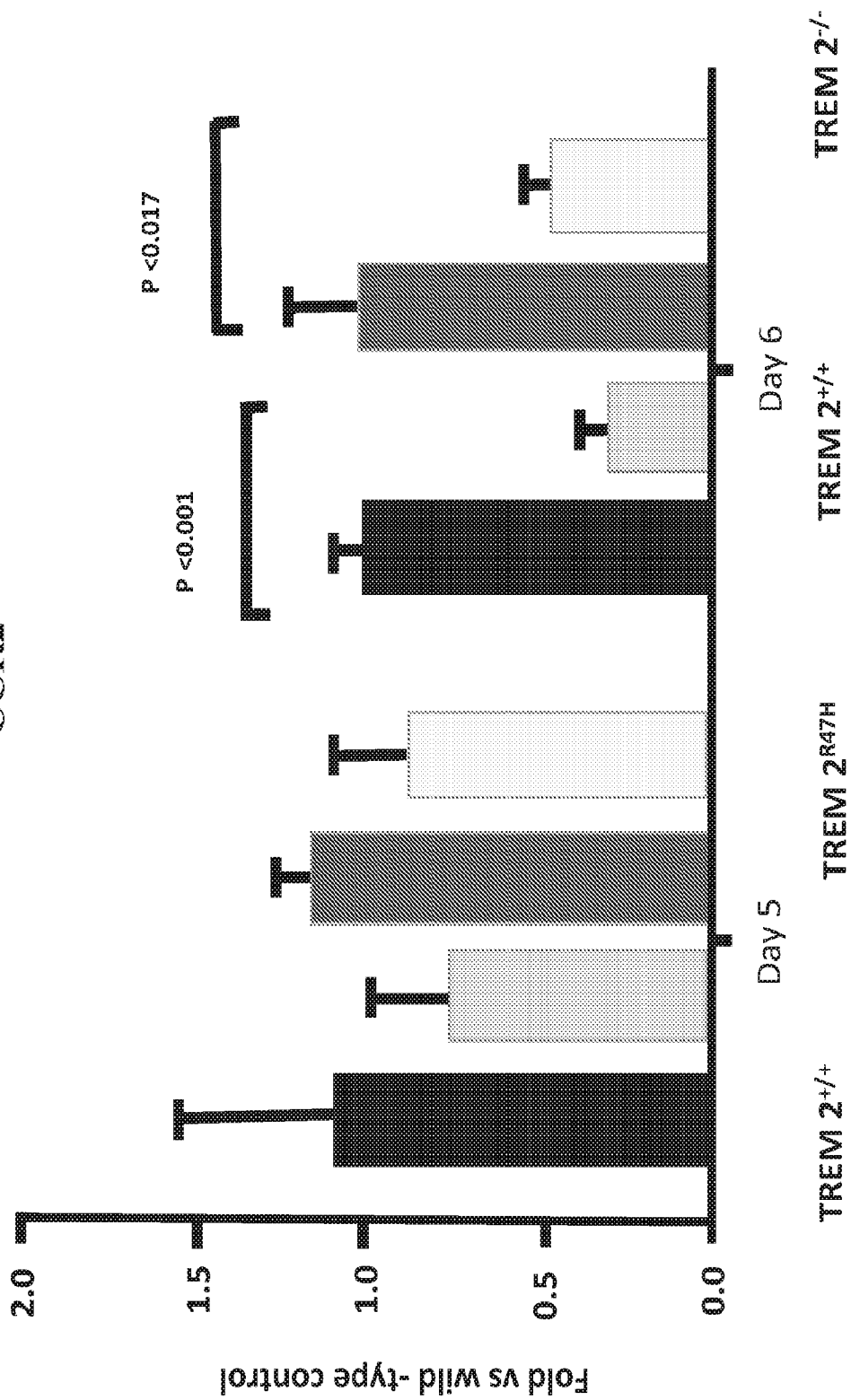


FIG. 12D

CCR2



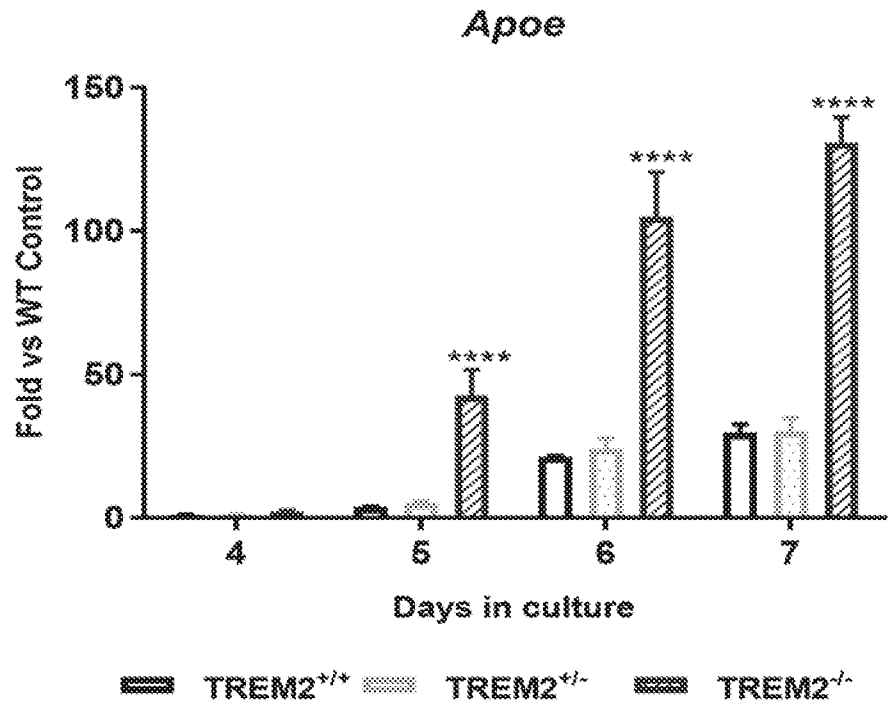


FIG. 13A

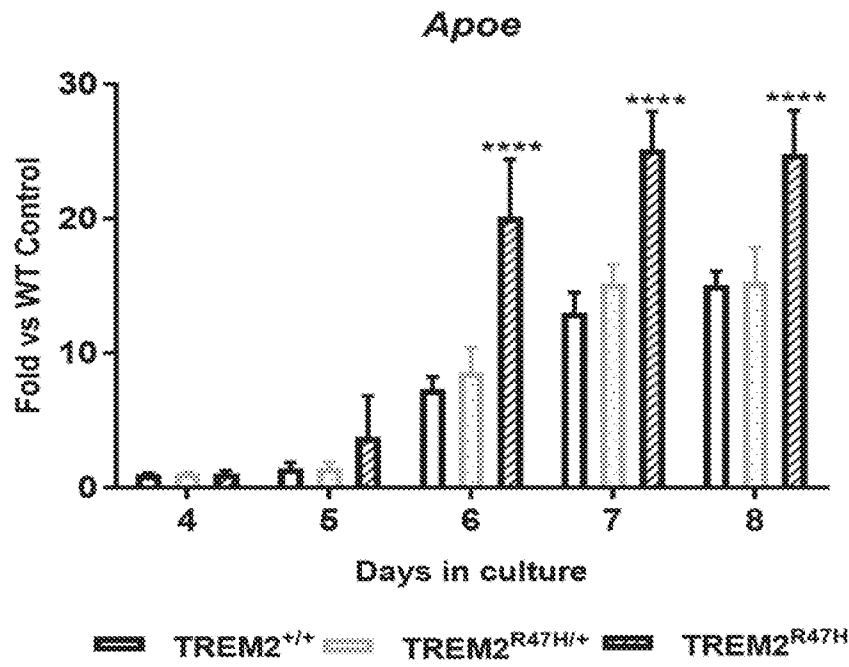


FIG. 13B

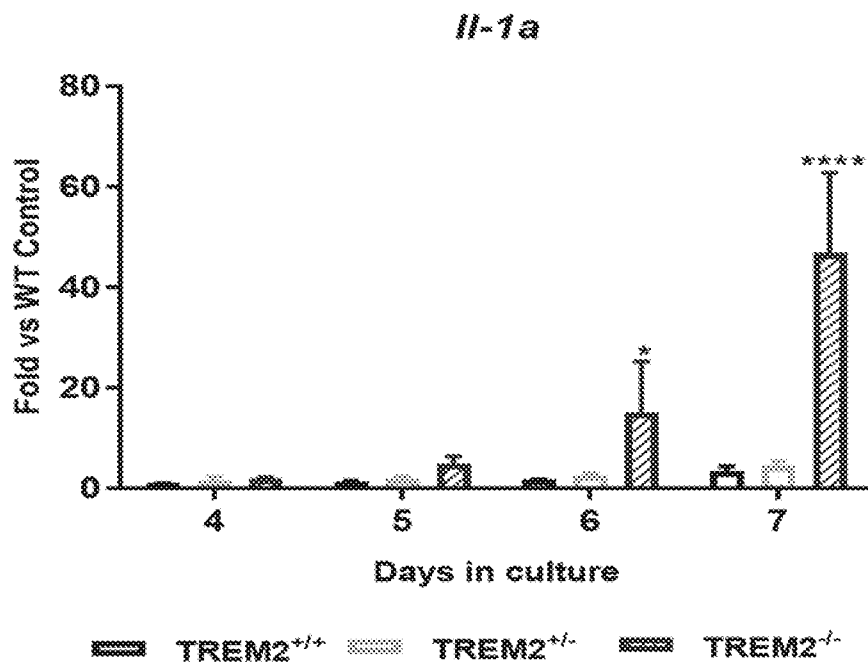


FIG. 13C

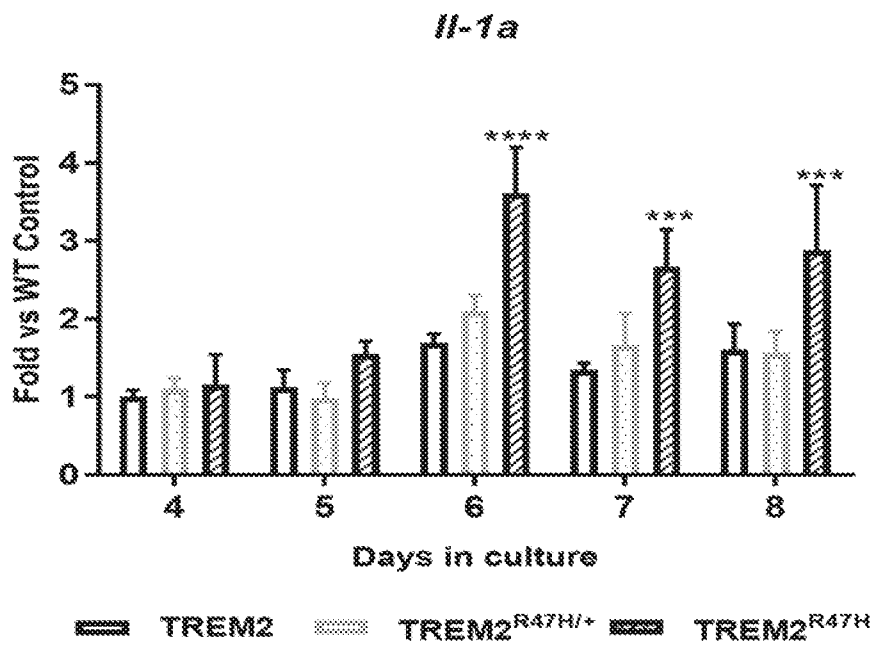


FIG. 13D

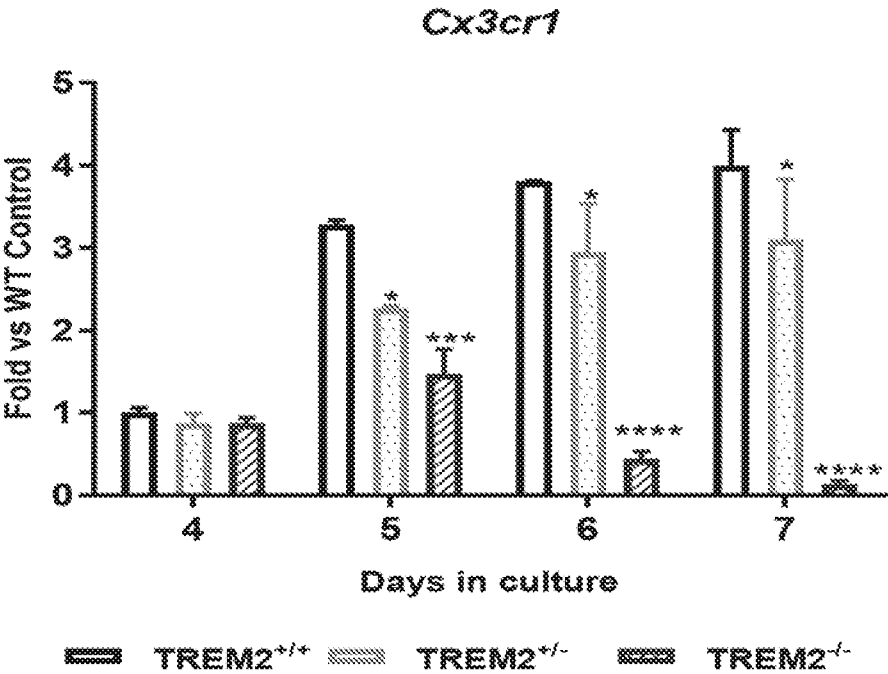


FIG. 13E

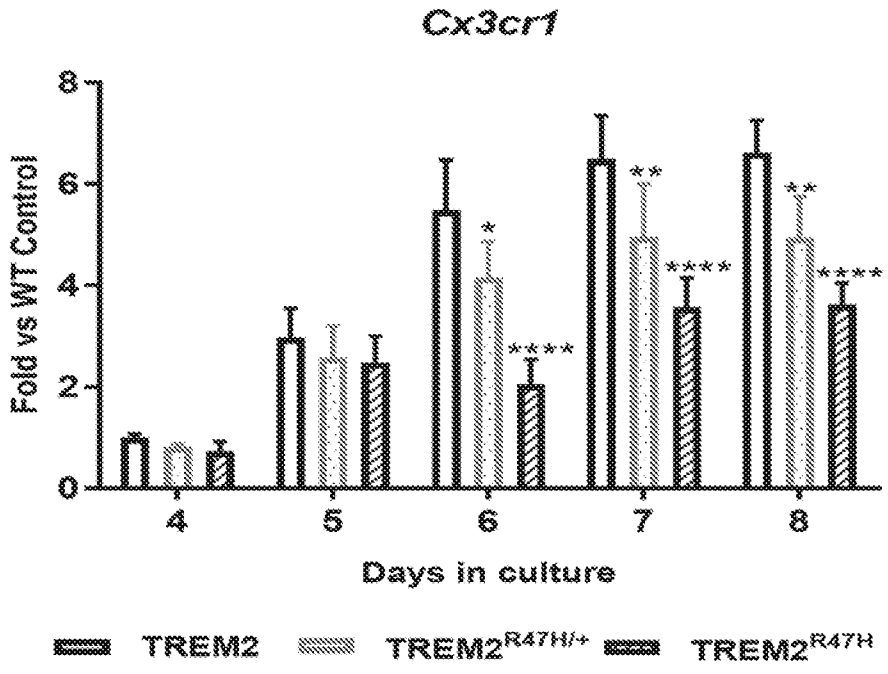


FIG. 13F

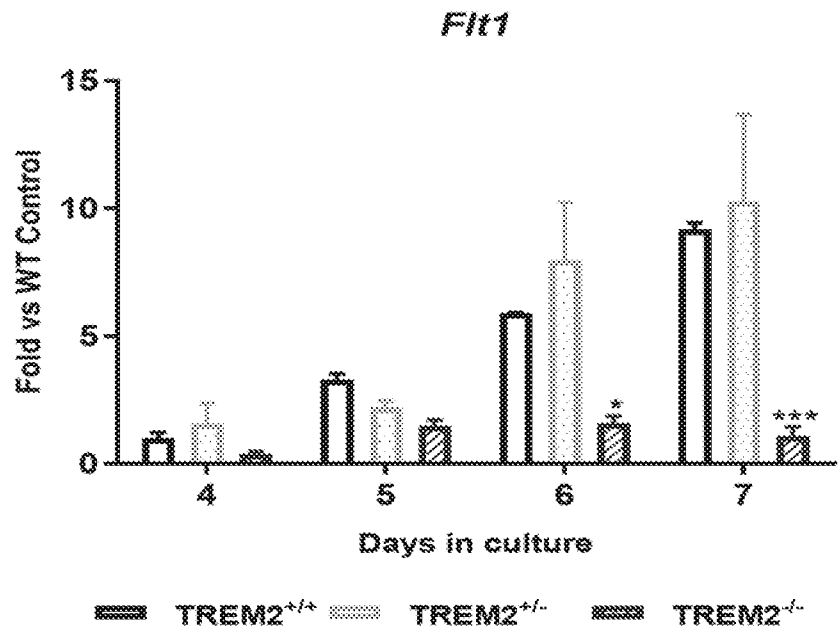


FIG. 13G

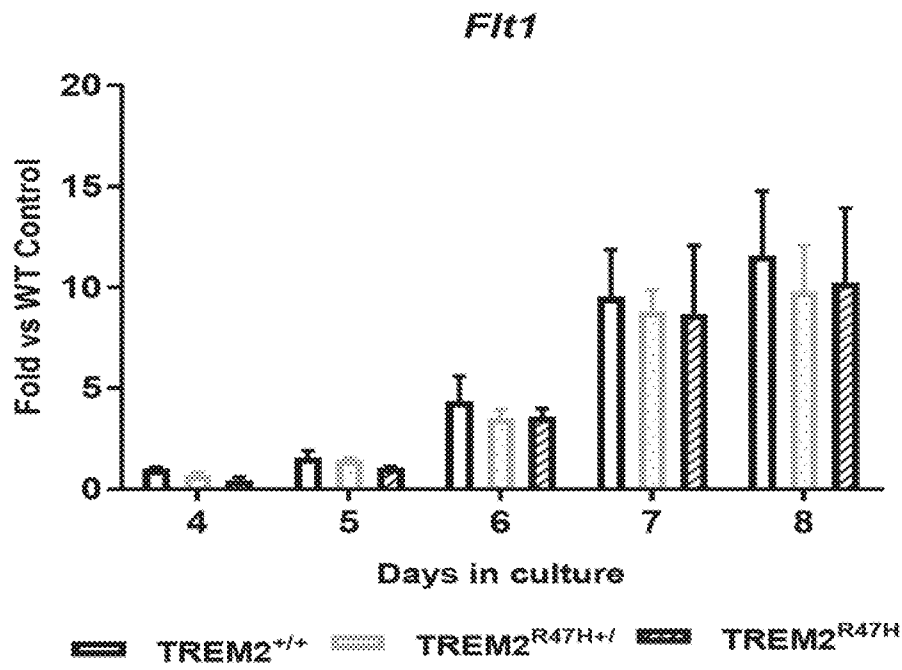


FIG. 13H

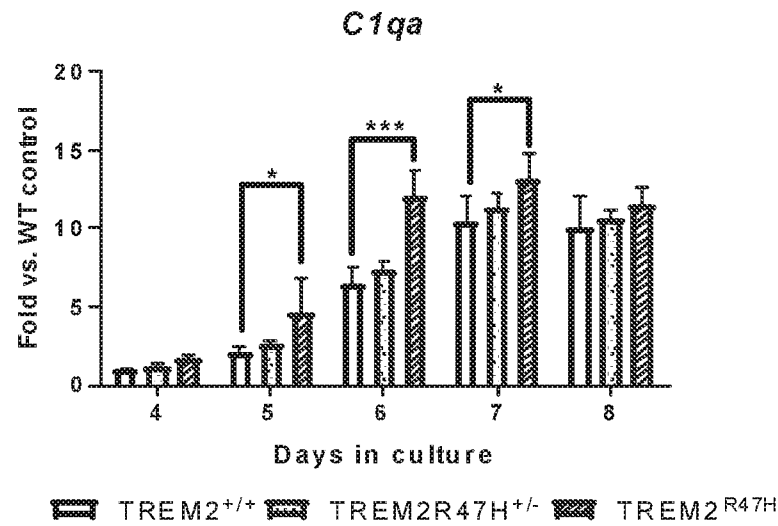


FIG. 13I

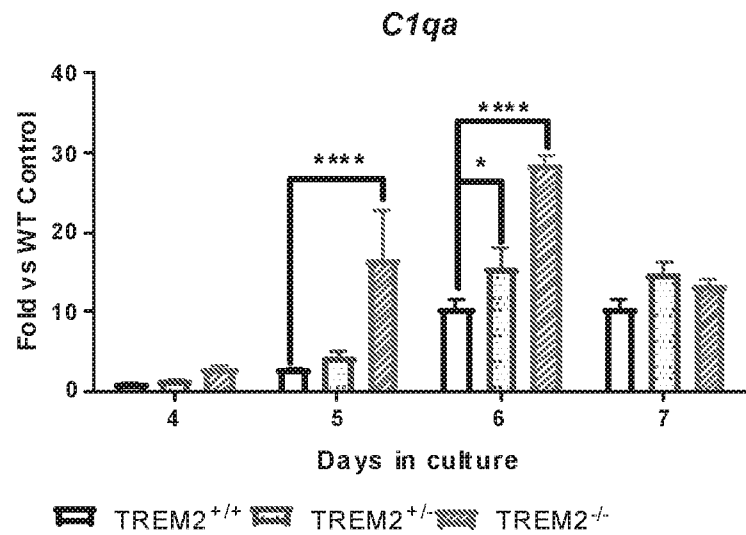


FIG. 13J

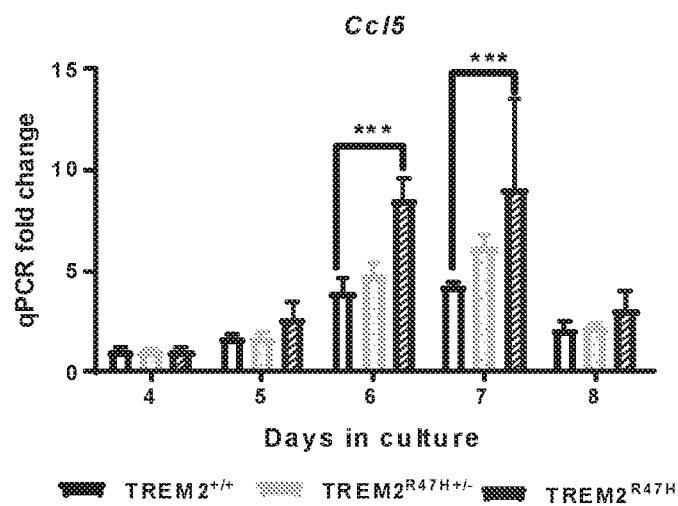


FIG. 13K

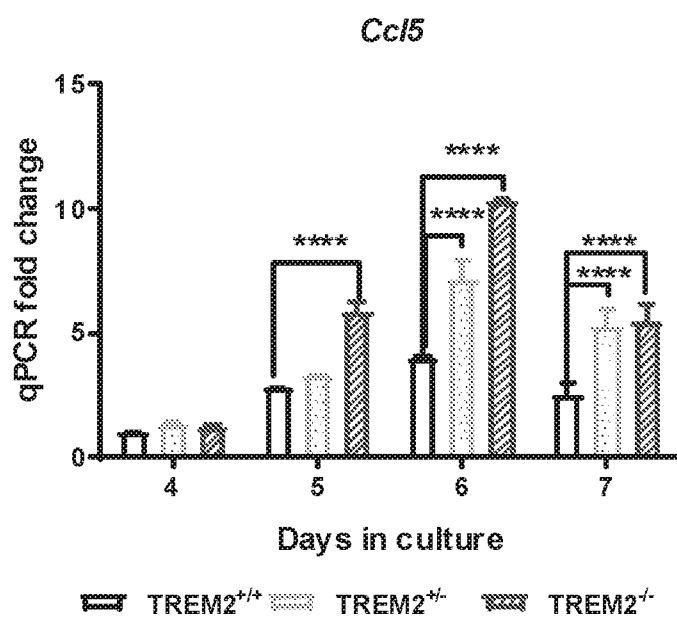


FIG. 13L

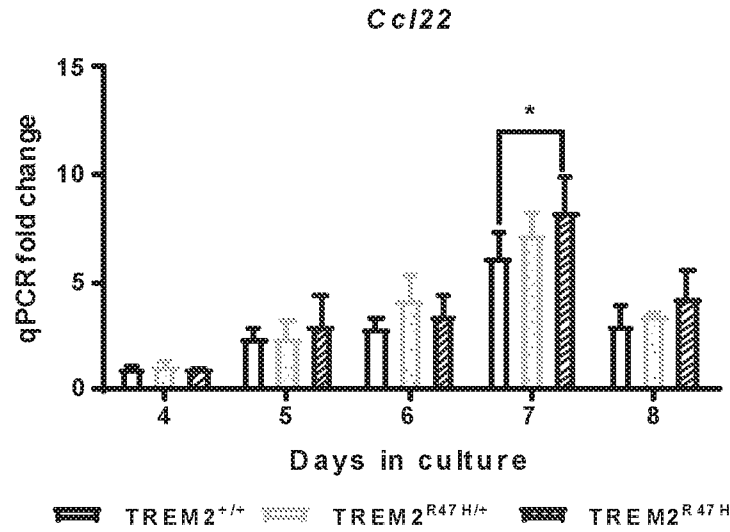


FIG. 13M

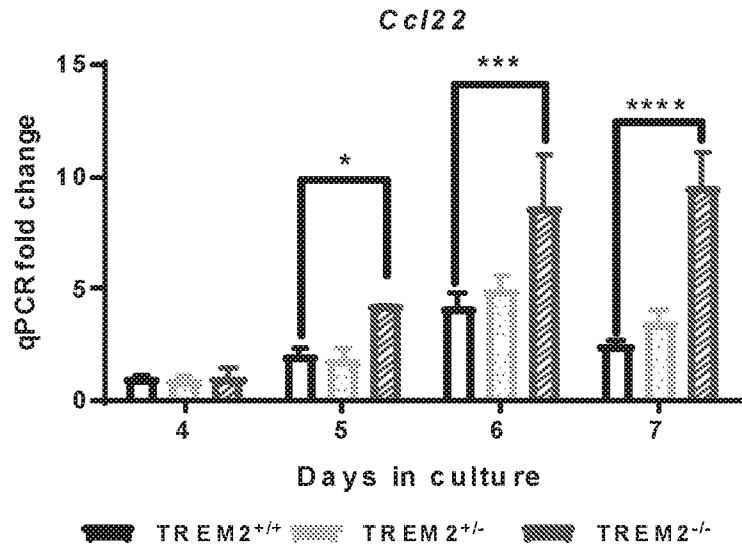


FIG. 13N

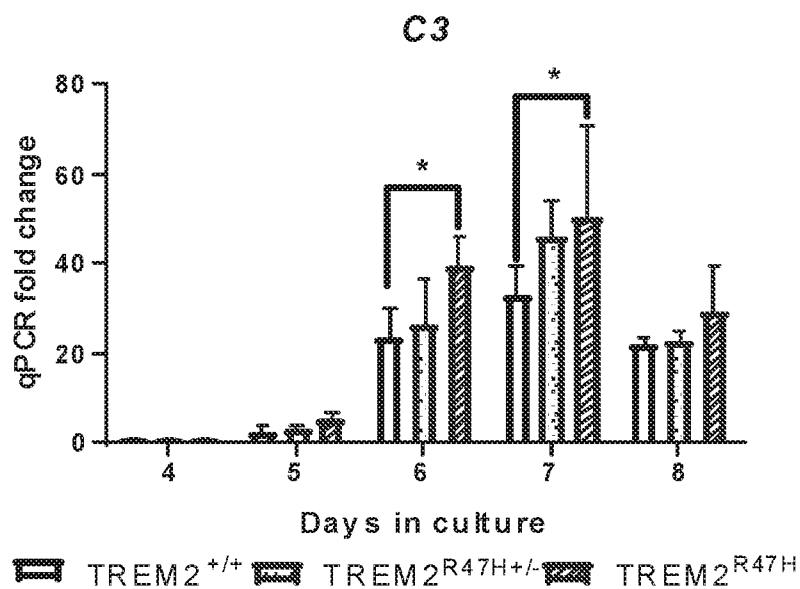


FIG. 13O

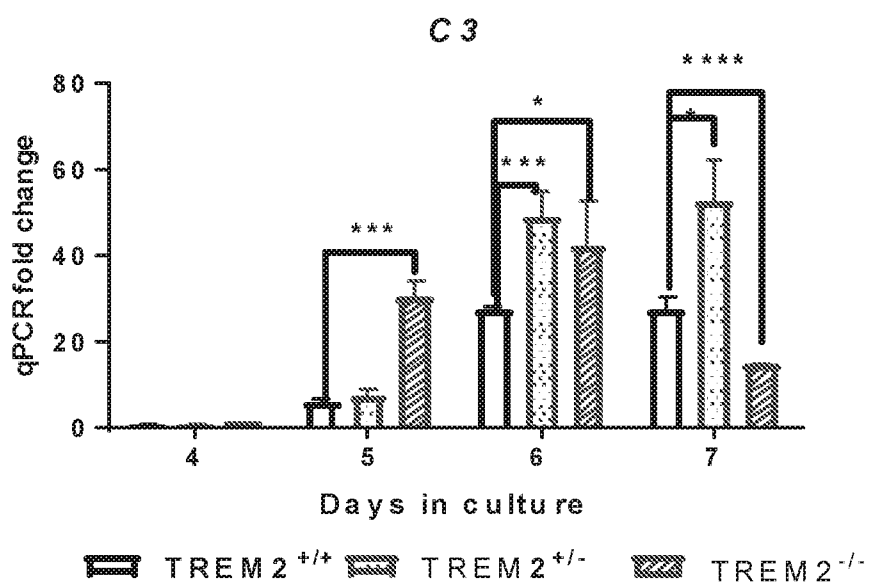


FIG. 13P

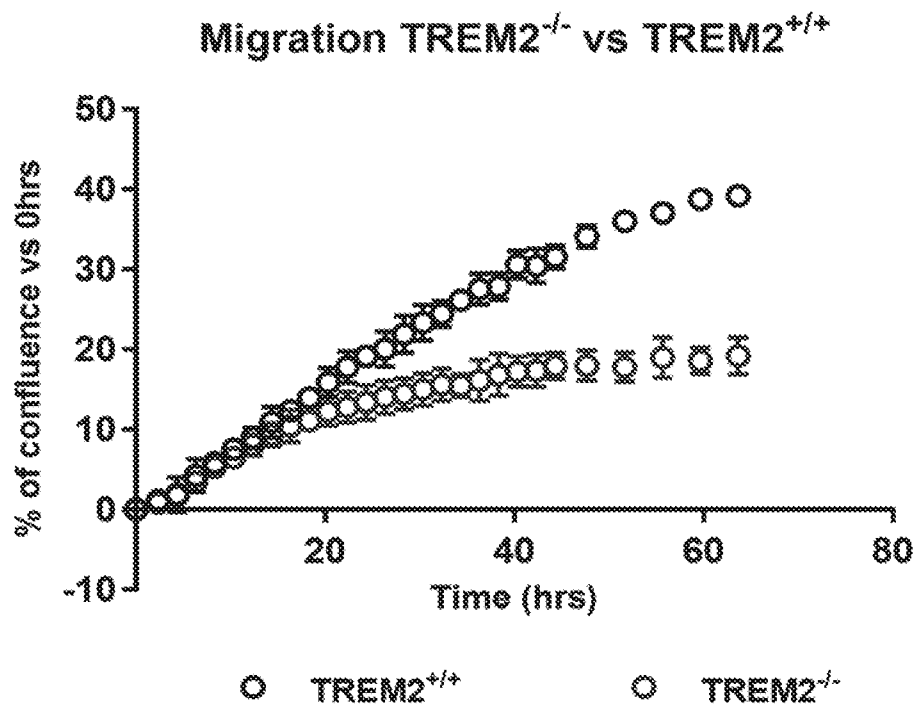


FIG. 14A

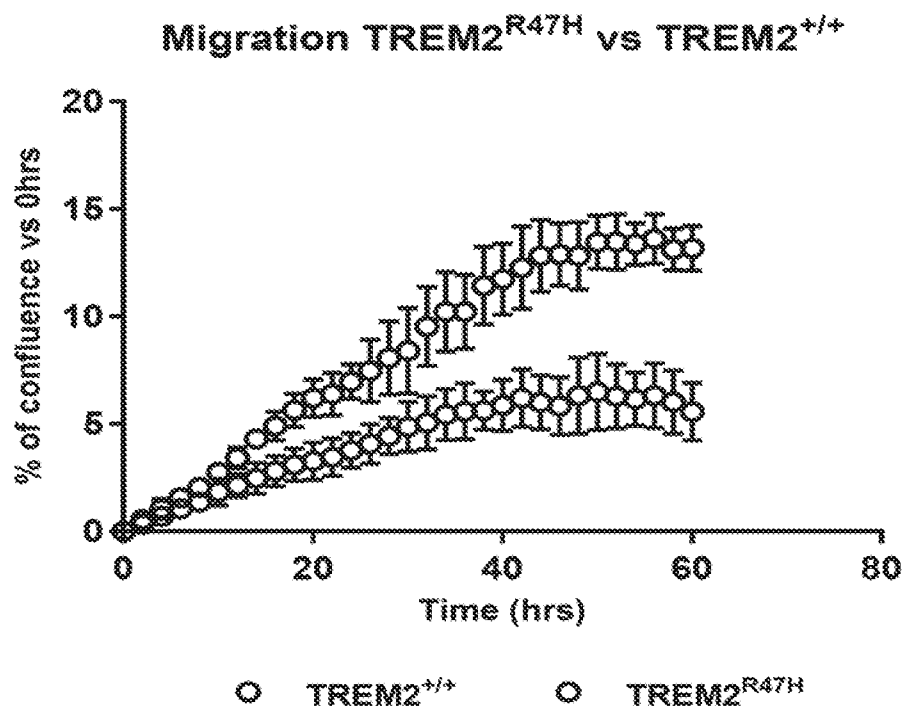


FIG. 14B

FIG. 15A

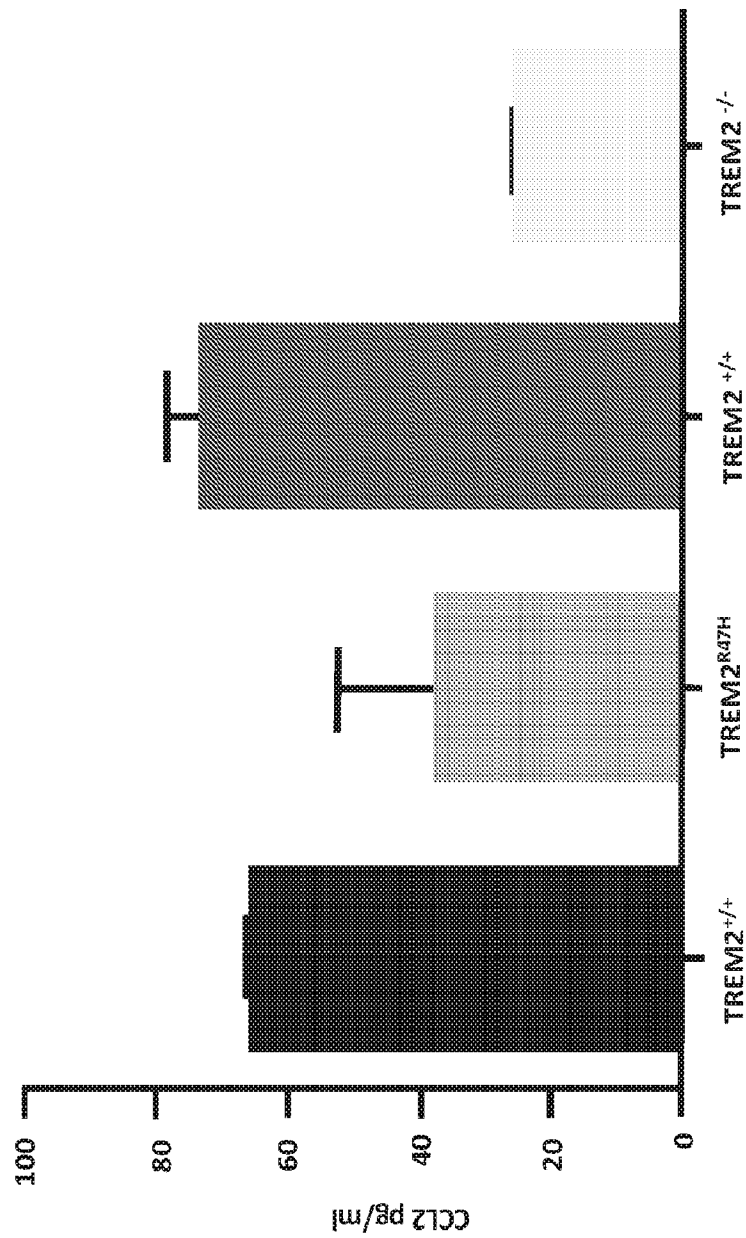
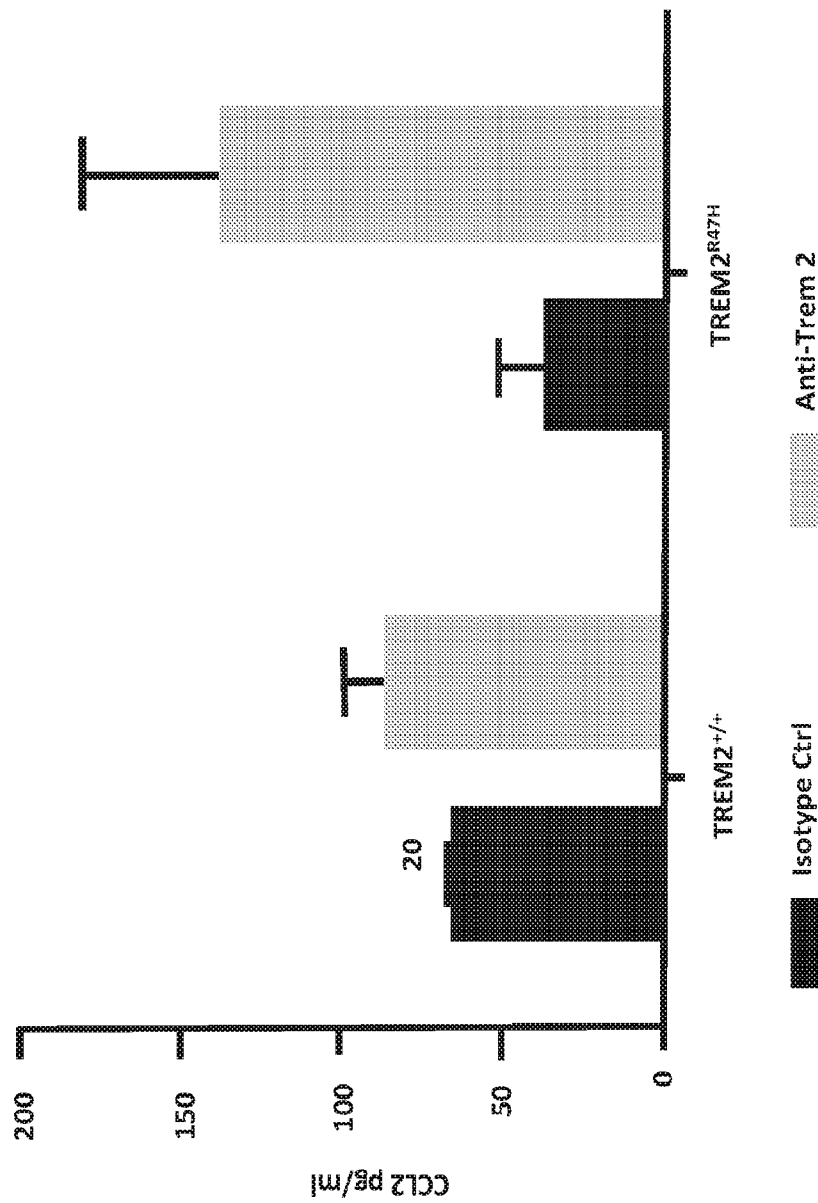
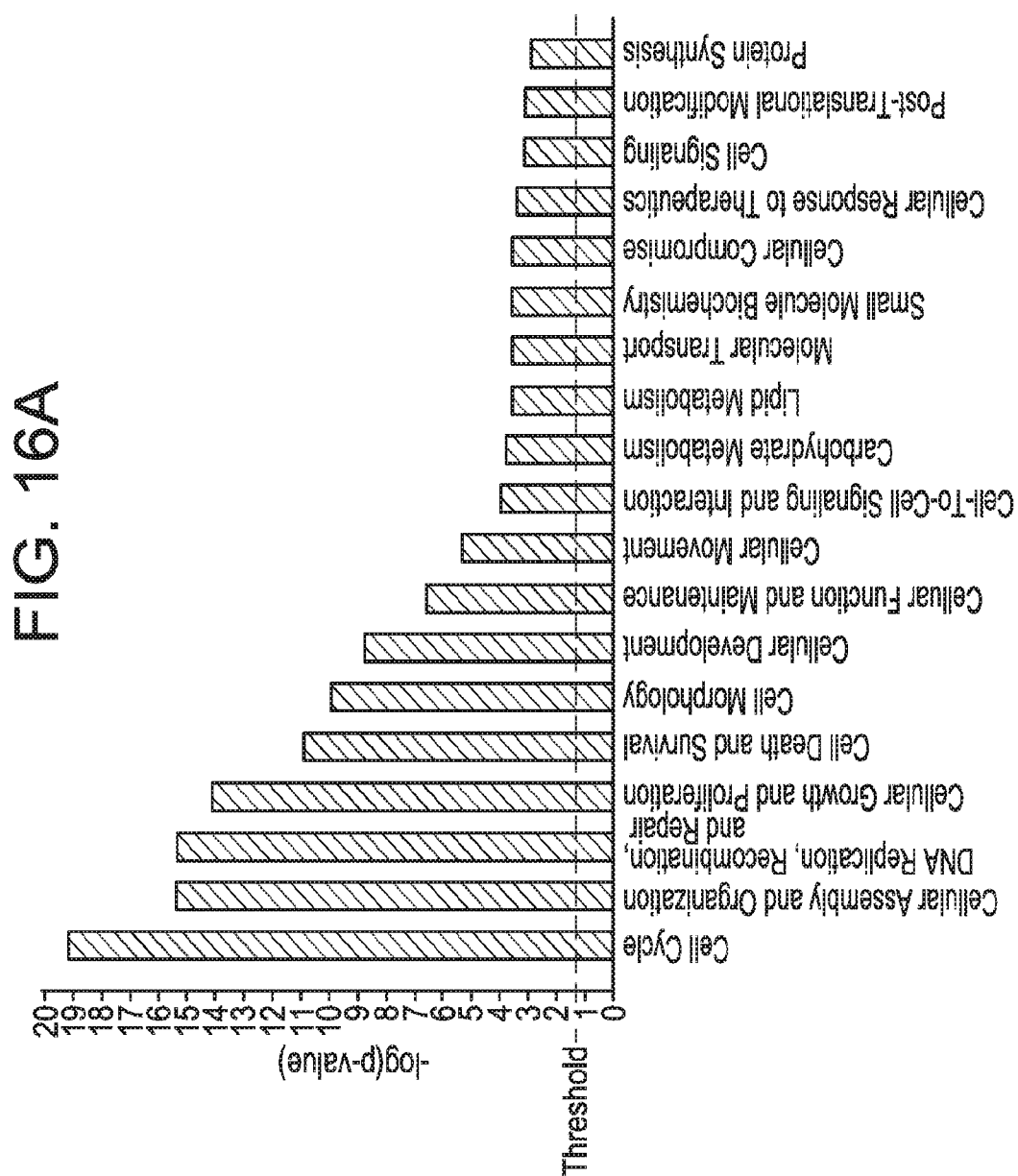


FIG. 15B





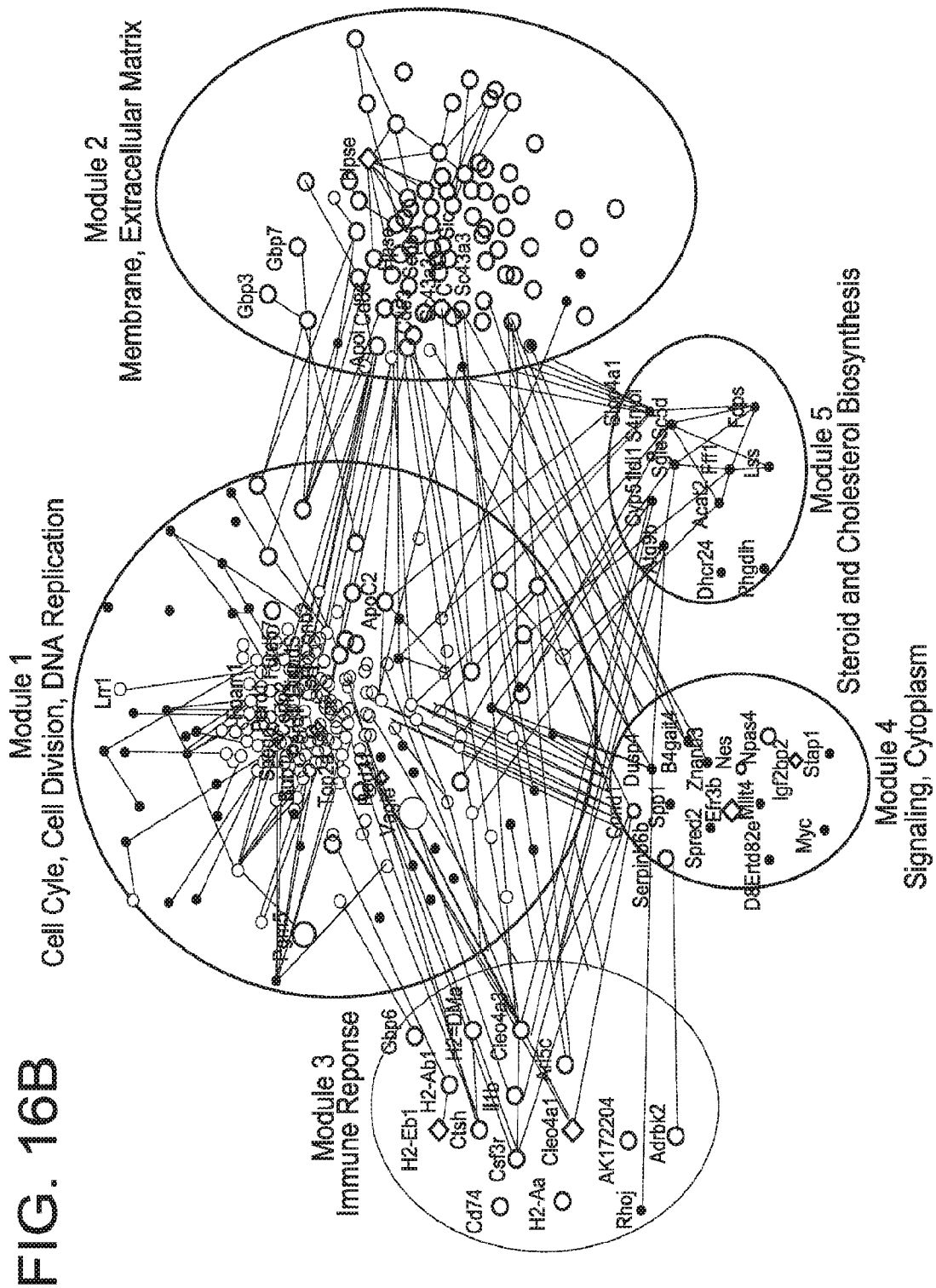


FIG. 16C

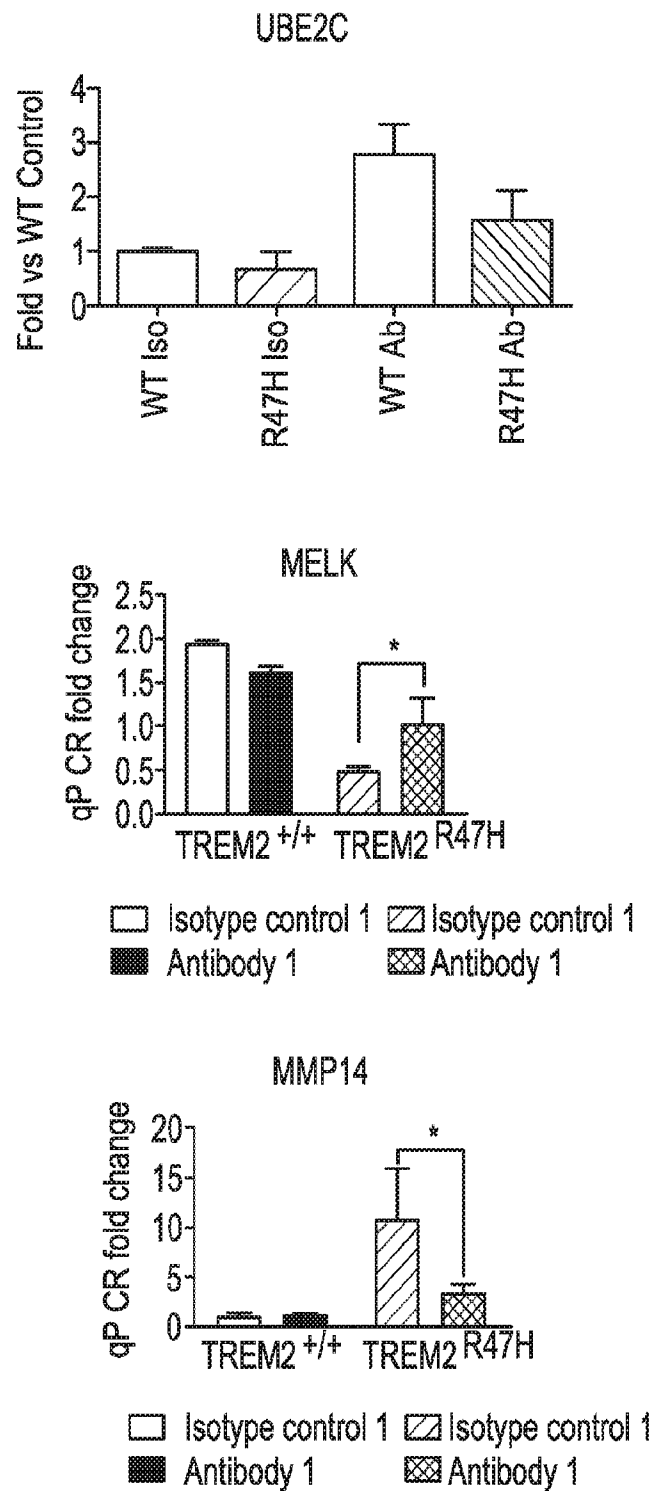


FIG. 17

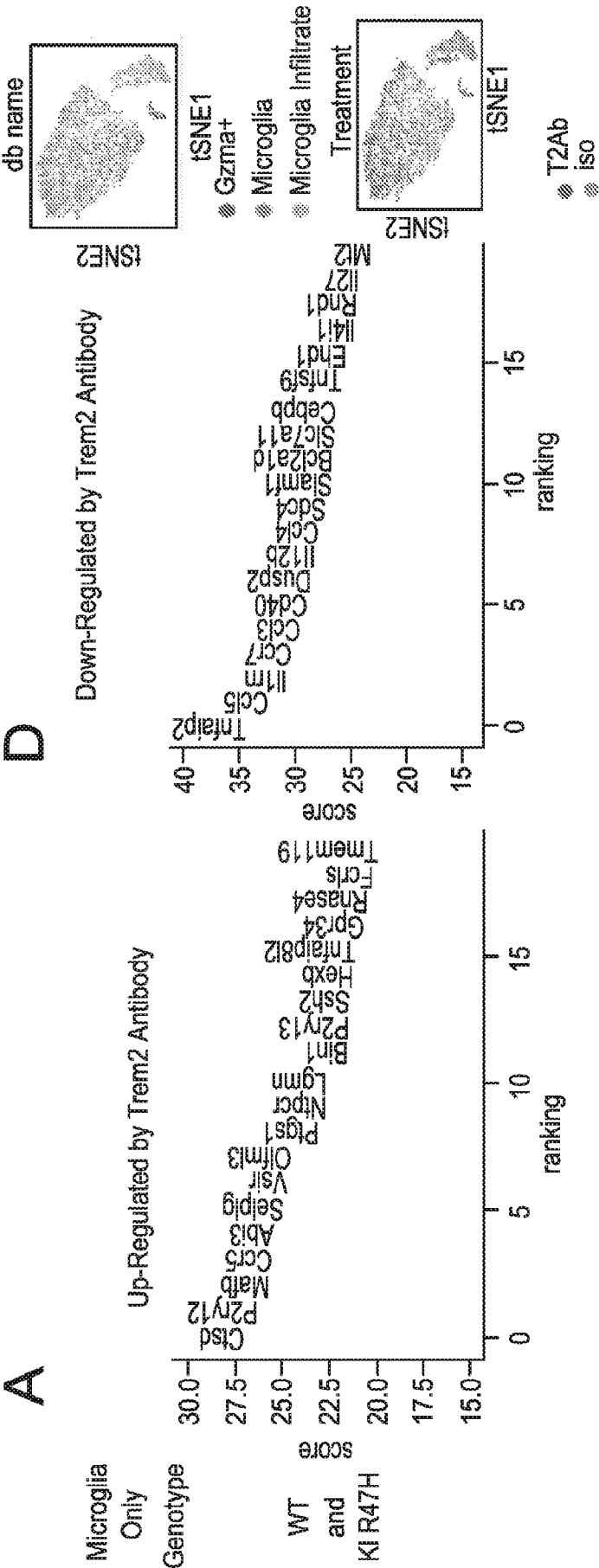


FIG. 17 Cont'd.

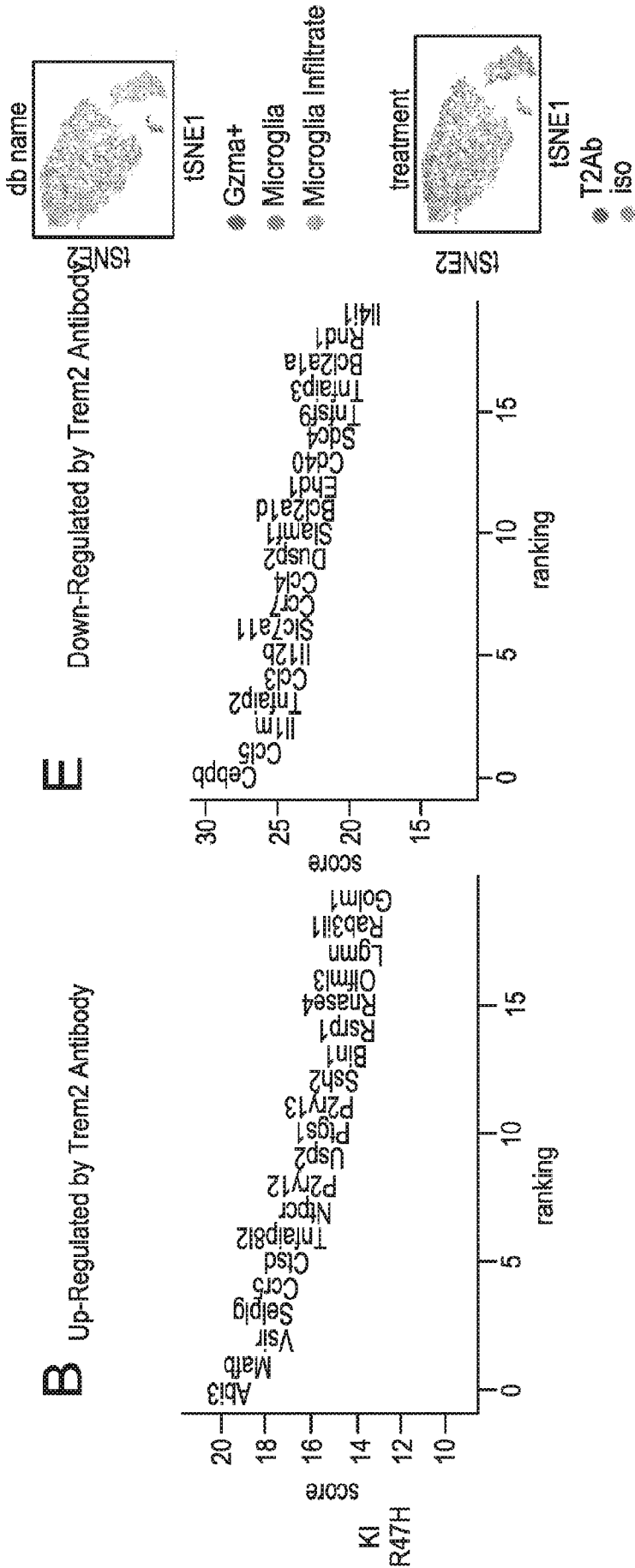


FIG. 17 Cont'd.

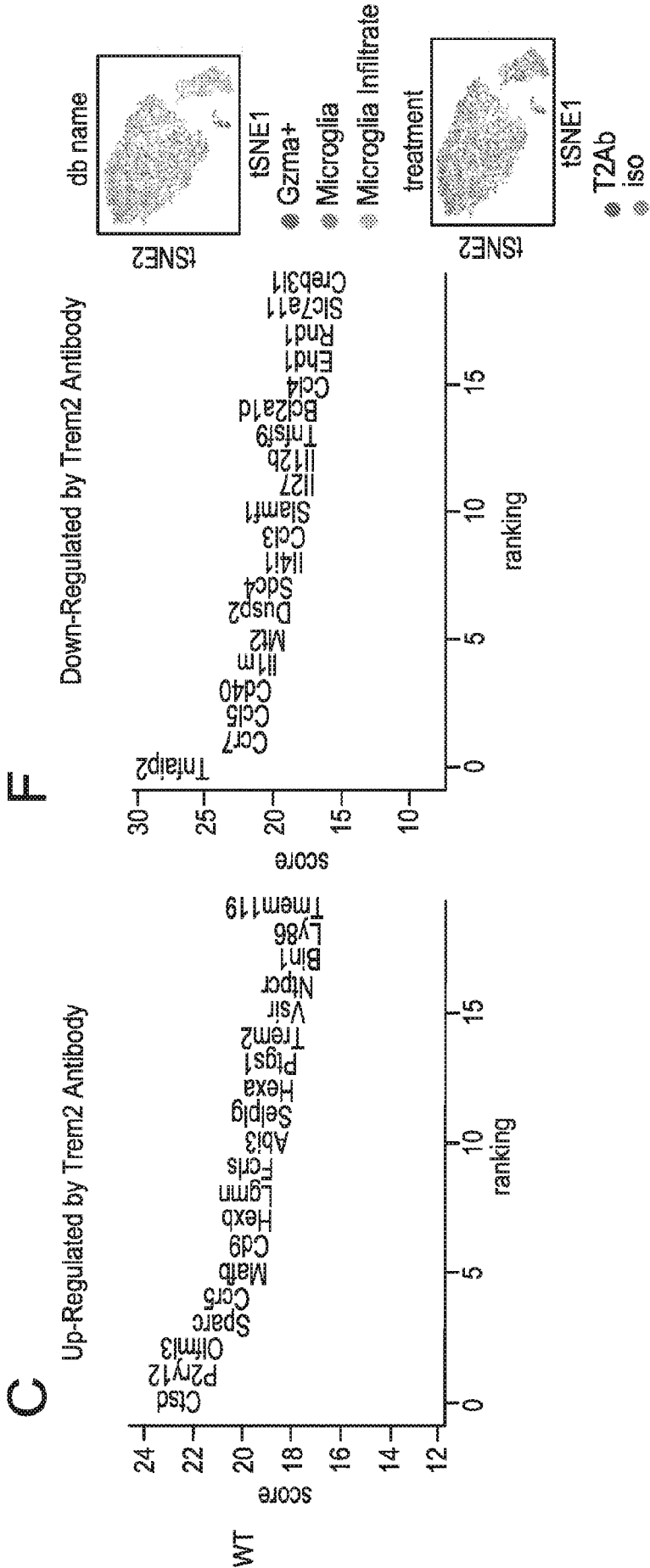


FIG. 18

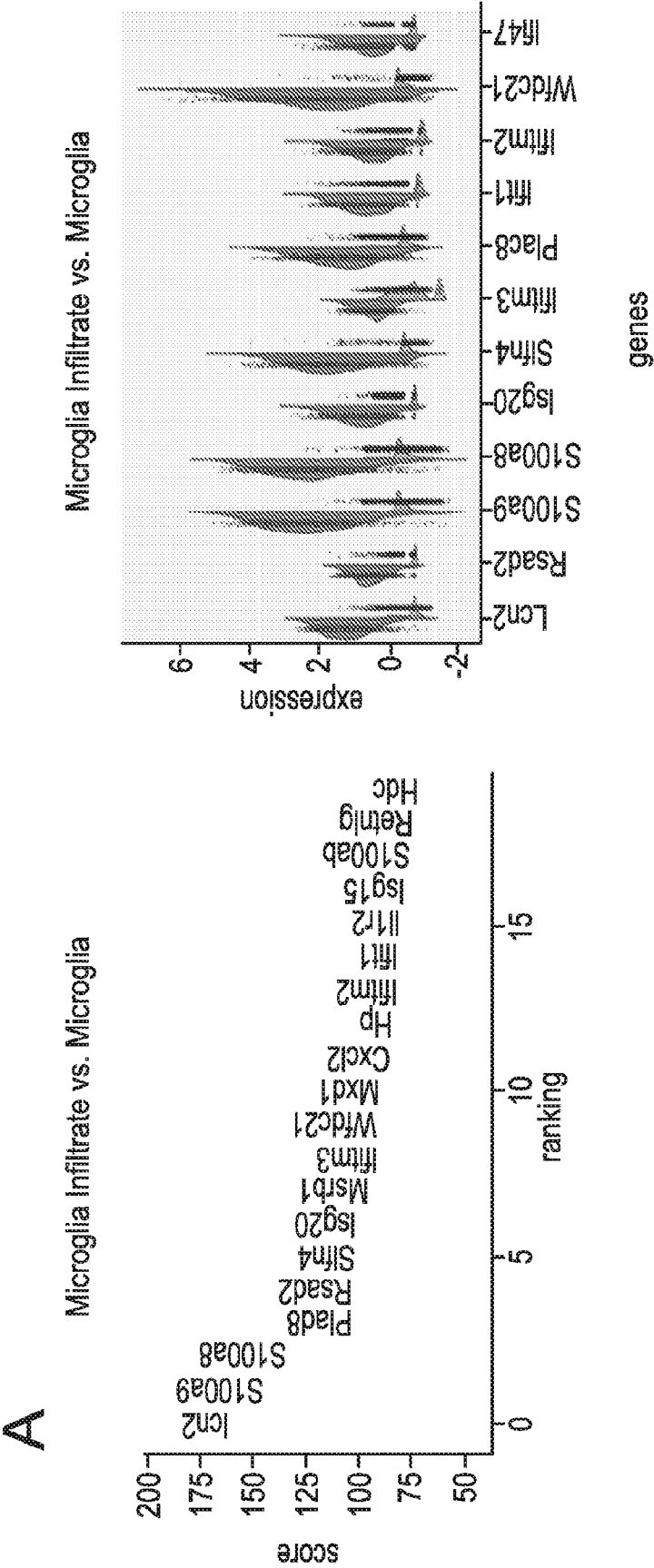


FIG. 18 Cont'd.

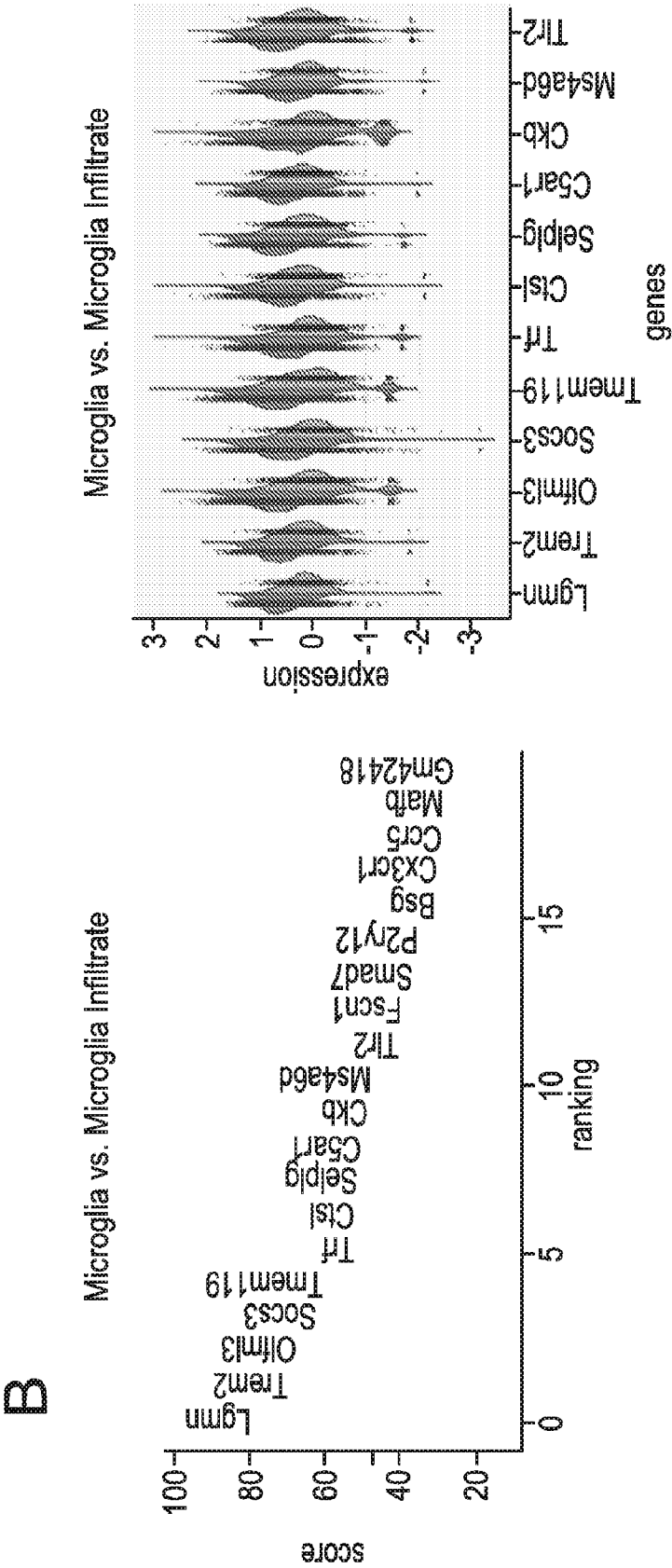


FIG. 18 Cont'd.

Infiltrate Population Only- WT & KI

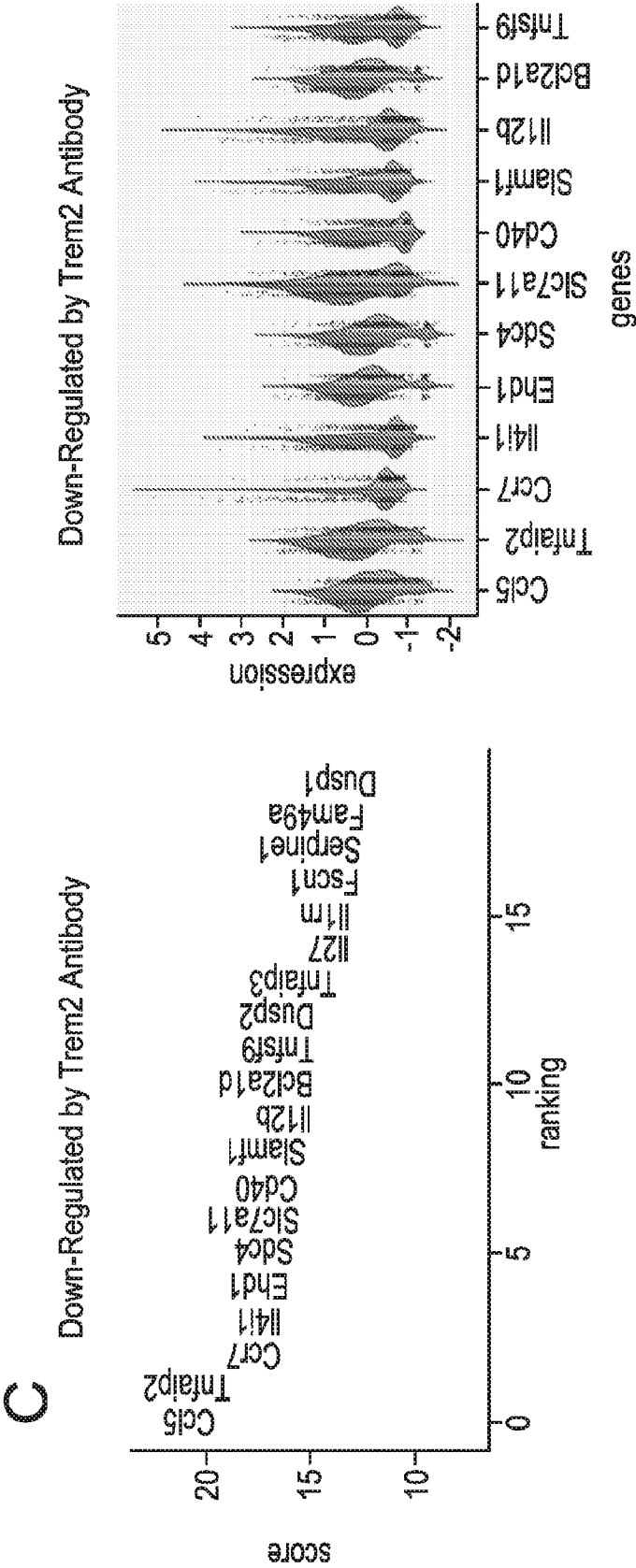


FIG. 18 Cont'd.
Infiltrate Population-WT Only

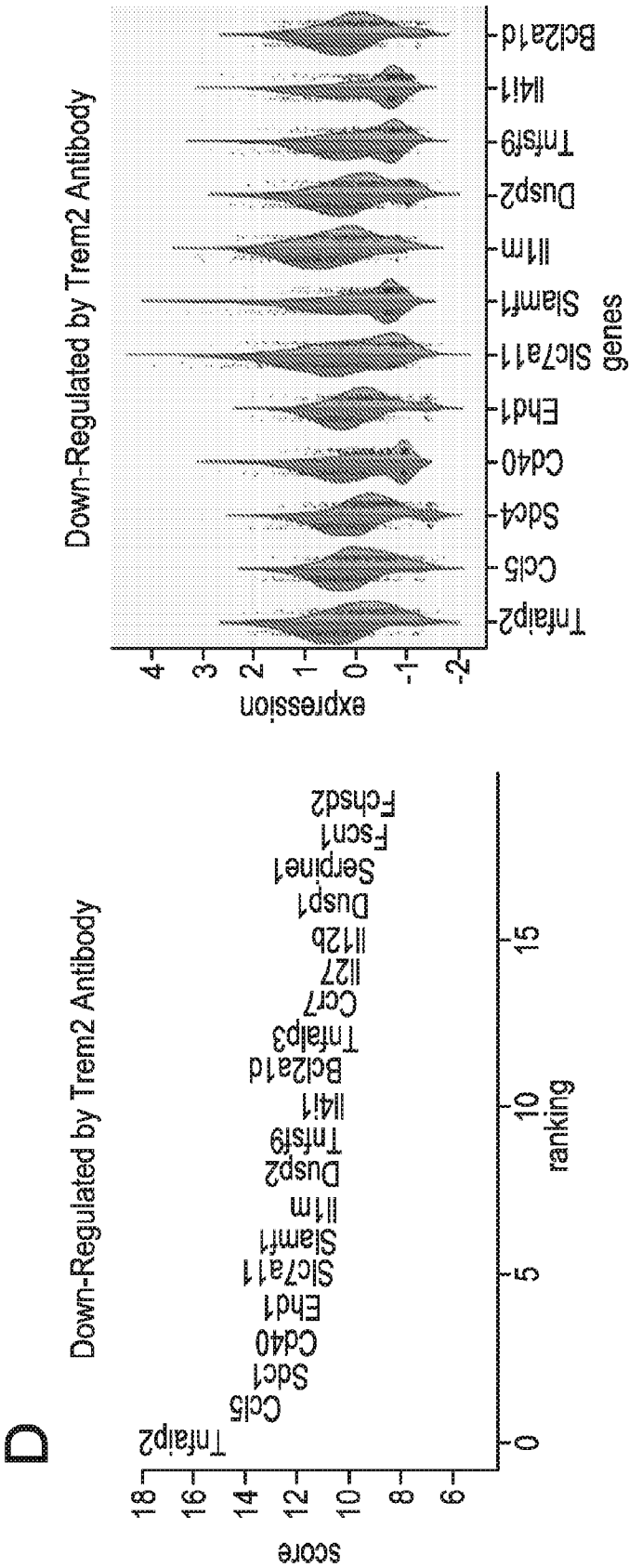
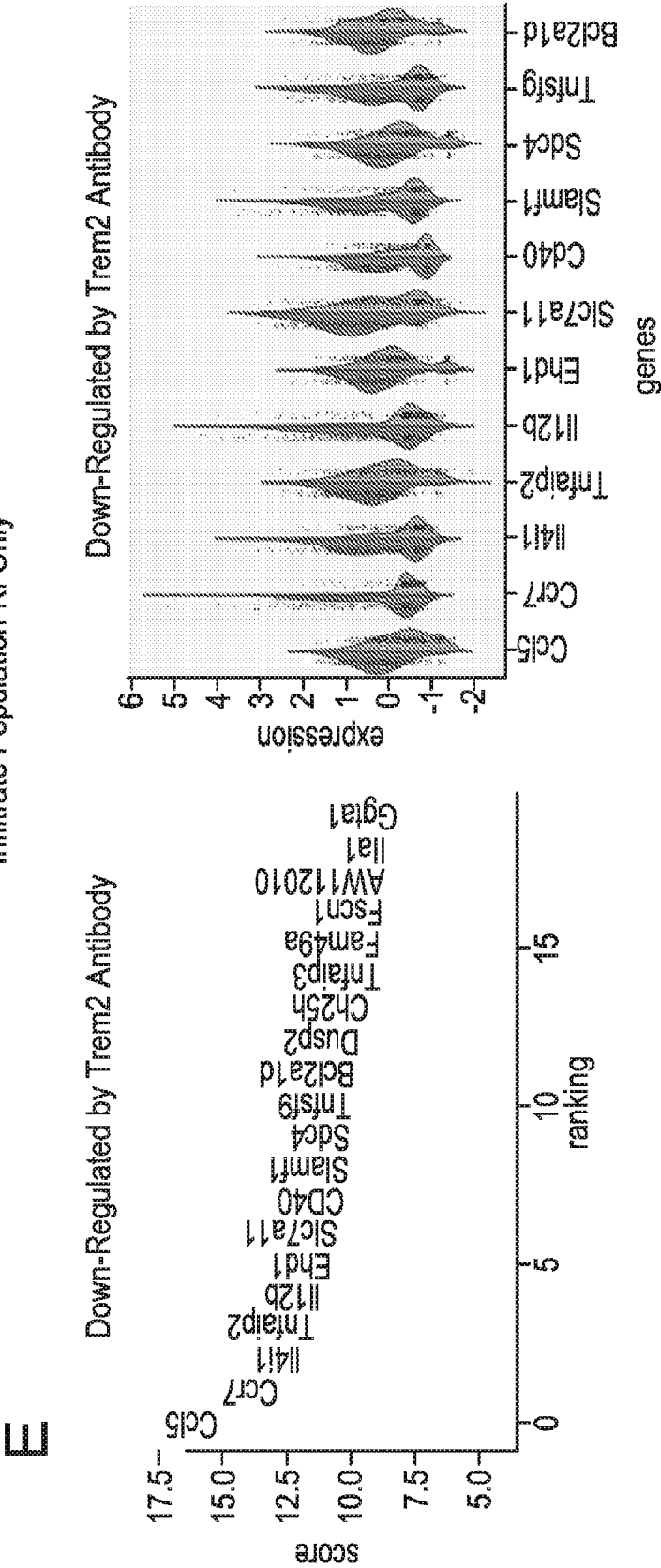


FIG. 18 Cont'd.

Infiltrate Population-KI Only



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<150> 62/488,691

<151> 2017-04-21

<150> 62/530,753

<151> 2017-07-10

<150> 62/580,400

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Ala Trp Cys Arg Gln Leu Gly Glu Lys Gly Pro Cys Gln Arg Val Val
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Ser Thr His Asn Leu Trp Leu Leu Ser Phe Leu Arg Arg Trp Asn Gly
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A-2129-W0-PCT_Sequence_Listing_ST25.txt

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Leu Ala Asp Pro Leu Asp His Arg Asp Ala Gly Asp Leu Trp Phe Pro
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Gly Glu Ser Glu Ser Phe Glu Asp Ala His Val Glu His Ser Ile Ser
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Arg Ser Leu Leu Glu Gly Glu Ile Pro Phe Pro Pro Thr Ser Ile Leu
165 170 175

Leu Leu Leu Ala Cys Ile Phe Leu Ile Lys Ile Leu Ala Ala Ser Ala
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Leu Trp Ala Ala Ala Trp His Gly Gln Lys Pro Gly Thr His Pro Pro
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Pro Gly Leu Arg Asp Thr
225 230

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A-2129-W0-PCT_Sequence_Listing_ST25.txt

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Ala Trp Cys Arg Gln Leu Gly Glu Lys Gly Pro Cys Gln Arg Val Val
50 55 60

Ser Thr His Asn Leu Trp Leu Leu Ser Phe Leu Arg Arg Trp Asn Gly
65 70 75 80

Ser Thr Ala Ile Thr Asp Asp Thr Leu Gly Gly Thr Leu Thr Ile Thr
85 90 95

Leu Arg Asn Leu Gln Pro His Asp Ala Gly Leu Tyr Gln Cys Gln Ser
100 105 110

Leu His Gly Ser Glu Ala Asp Thr Leu Arg Lys Val Leu Val Glu Val
115 120 125

Leu Ala Asp Pro Leu Asp His Arg Asp Ala Gly Asp Leu Trp Phe Pro
130 135 140

Gly Glu Ser Glu Ser Phe Glu Asp Ala His Val Glu His Ser Ile Ser
145 150 155 160

Arg Ser Leu Leu Glu Gly Glu Ile Pro Phe Pro Pro Thr Ser
165 170

<210> 3
<211> 113
<212> PRT
<213> Homo sapiens

<400> 3

Met Gly Gly Leu Glu Pro Cys Ser Arg Leu Leu Leu Leu Pro Leu Leu
1 5 10 15

Leu Ala Val Ser Gly Leu Arg Pro Val Gln Ala Gln Ala Gln Ser Asp
20 25 30

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Cys Ser Cys Ser Thr Val Ser Pro Gly Val Leu Ala Gly Ile Val Met
35 40 45

Gly Asp Leu Val Leu Thr Val Leu Ile Ala Leu Ala Val Tyr Phe Leu
50 55 60

Gly Arg Leu Val Pro Arg Gly Arg Gly Ala Ala Glu Ala Ala Thr Arg
65 70 75 80

Lys Gln Arg Ile Thr Glu Thr Glu Ser Pro Tyr Gln Glu Leu Gln Gly
85 90 95

Gln Arg Ser Asp Val Tyr Ser Asp Leu Asn Thr Gln Arg Pro Tyr Tyr
100 105 110

Lys

<210> 4
<211> 234
<212> PRT
<213> Homo sapiens

<400> 4

Met Arg Lys Thr Arg Leu Trp Gly Leu Leu Trp Met Leu Phe Val Ser
1 5 10 15

Glu Leu Arg Ala Ala Thr Lys Leu Thr Glu Glu Lys Tyr Glu Leu Lys
20 25 30

Glu Gly Gln Thr Leu Asp Val Lys Cys Asp Tyr Thr Leu Glu Lys Phe
35 40 45

Ala Ser Ser Gln Lys Ala Trp Gln Ile Ile Arg Asp Gly Glu Met Pro
50 55 60

Lys Thr Leu Ala Cys Thr Glu Arg Pro Ser Lys Asn Ser His Pro Val
65 70 75 80

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Gln Val Gly Arg Ile Ile Leu Glu Asp Tyr His Asp His Gly Leu Leu
85 90 95

Arg Val Arg Met Val Asn Leu Gln Val Glu Asp Ser Gly Leu Tyr Gln
100 105 110

Cys Val Ile Tyr Gln Pro Pro Lys Glu Pro His Met Leu Phe Asp Arg
115 120 125

Ile Arg Leu Val Val Thr Lys Gly Phe Ser Gly Thr Pro Gly Ser Asn
130 135 140

Glu Asn Ser Thr Gln Asn Val Tyr Lys Ile Pro Pro Thr Thr Thr Lys
145 150 155 160

Ala Leu Cys Pro Leu Tyr Thr Ser Pro Arg Thr Val Thr Gln Ala Pro
165 170 175

Pro Lys Ser Thr Ala Asp Val Ser Thr Pro Asp Ser Glu Ile Asn Leu
180 185 190

Thr Asn Val Thr Asp Ile Ile Arg Val Pro Val Phe Asn Ile Val Ile
195 200 205

Leu Leu Ala Gly Gly Phe Leu Ser Lys Ser Leu Val Phe Ser Val Leu
210 215 220

Phe Ala Val Thr Leu Arg Ser Phe Val Pro
225 230

<210> 5

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> CRDL1 Antibody ID 12G10

<400> 5

Thr Leu Arg Ser Gly Ile Asn Val Gly Thr Tyr Arg Ile Tyr
1 5 10

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 6
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 Antibody ID 26C10

<400> 6

Ser Gly Asp Lys Leu Gly Asp Lys Tyr Val Cys
1 5 10

<210> 7
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 Antibody ID 24C12

<400> 7

Lys Ser Ser Arg Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 8
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 Antibody ID 24G6

<400> 8

Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Asn Lys His Phe Leu
1 5 10 15

Ala

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 9

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL1 Antibody ID 24A10

<400> 9

Lys	Ser	Ser	His	Asn	Val	Leu	Tyr	Ser	Ser	Asn	Asn	Lys	Asn	Tyr	Leu
1				5				10					15		

Ala

<210> 10

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL1 Antibody ID 10E3

<400> 10

Arg	Ala	Ser	Gln	Ser	Val	Ser	Ser	Asn	Leu	Ala
1				5				10		

<210> 11

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL1 Antibody ID 25F12

<400> 11

Arg	Ala	Ser	Gln	Ser	Val	Asn	Asn	Asn	Leu	Ala
1				5				10		

<210> 12

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL1 Antibody ID 32E3

<400> 12

Arg	Ala	Ser	Gln	Ile	Ile	Ser	Ser	Asn	Tyr	Leu	Ala
1				5					10		

<210> 13

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL1 Antibody ID 24F4

<400> 13

Arg	Ala	Ser	Gln	Ser	Val	Ser	Ser	Ser	Tyr	Leu	Ala
1				5					10		

<210> 14

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL1 Antibody ID 16B8

<400> 14

Arg	Ala	Ser	Gln	Asp	Ile	Asn	Ser	Trp	Leu	Ala
1				5					10	

<210> 15

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL1 Antibody ID 4C5

<400> 15

Arg	Ala	Ser	Gln	Gly	Ile	Ser	Asn	Trp	Leu	Ala
1				5					10	

<210> 16

<211> 11

<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 Antibody ID 6E7

<400> 16

Arg	Ala	Ser	Gln	Gly	Ile	Ser	Ser	Trp	Leu	Ala
1				5					10	

<210> 17
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 Antibody ID 5E3

<400> 17

Arg	Ala	Ser	Gln	Gly	Ile	Ser	Asn	Tyr	Leu	Ala
1				5					10	

<210> 18
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 Antibody ID 4G10

<400> 18

Arg	Ala	Ser	Gln	Gly	Ile	Arg	Asn	Asp	Leu	Gly
1				5					10	

<210> 19
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL2 Antibody ID 12G10

<400> 19

Tyr	Lys	Ser	Asp	Ser	Asp	Lys	Gln	Gln	Gly	Ser
1				5					10	

<210> 20
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRL2 Antibody ID 26C10

<400> 20

Gln Asp Ser Lys Arg Pro Ser
 1 5

<210> 21
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRL2 Antibody ID 26C10

<400> 21

Gln Asp Thr Lys Arg Pro Ser
 1 5

<210> 22
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRL2 Antibody ID 24C12

<400> 22

Trp Ala Ser Thr Arg Glu Ser
 1 5

<210> 23
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRL2 Antibody ID 10E3

<400> 23

Gly Ala Ser Thr Arg Ala Thr
1 5

<210> 24

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL2 Antibody ID 32E3

<400> 24

Ser Ala Ser Ser Arg Ala Thr
1 5

<210> 25

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL2 Antibody ID 24F4

<400> 25

Gly Ala Ser Ser Arg Ala Thr
1 5

<210> 26

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL2 Antibody ID 16B8

<400> 26

Ala Ala Ser Ser Leu Gln Thr
1 5

<210> 27

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL2 Antibody ID 4C5

<400> 27

Ala Ala Ser Ser Leu Gln Val
1 5

<210> 28

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL2 Antibody ID 6E7

<400> 28

Ala Ala Ser Ser Leu Gln Asn
1 5

<210> 29

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL2 Antibody ID 5E3

<400> 29

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 30

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL2 Antibody ID 4G10

<400> 30

Ala Ala Ser Ser Leu Pro Ser
1 5

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 31

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL3 Antibody ID 12G10

<400> 31

Met Ile Trp Tyr Ser Ser Ala Val Val
1 5

<210> 32

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL3 Antibody ID 26A10

<400> 32

Gln Ala Trp Asp Ser Asn Thr Val Val
1 5

<210> 33

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL3 Antibody ID 26C10

<400> 33

Gln Ala Trp Asp Ser Ser Thr Val Val
1 5

<210> 34

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL3 Antibody ID 24C12

<400> 34

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Gln Gln Tyr Tyr Ile Thr Pro Ile Thr
1 5

<210> 35
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL3 Antibody ID 24G6

<400> 35

Gln Gln Tyr Tyr Ser Thr Pro Leu Thr
1 5

<210> 36
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL3 Antibody 24A10

<400> 36

His Gln Tyr Tyr Ser Thr Pro Cys Ser
1 5

<210> 37
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL3 Antibody ID 10E3

<400> 37

Leu Gln Asp Asn Asn Trp Pro Pro Thr
1 5

<210> 38
<211> 9
<212> PRT
<213> Artificial Sequence

<220>

<223> CDRL3 Antibody ID 25F12

<400> 38

Gln Gln Tyr Asn Asn Trp Pro Arg Thr
1 5

<210> 39

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL3 Antibody ID 32E3

<400> 39

Gln Gln Phe Asp Ser Ser Pro Ile Thr
1 5

<210> 40

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL3 Antibody ID 24F4

<400> 40

Gln Gln Tyr Asp Thr Ser Pro Phe Thr
1 5

<210> 41

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL3 Antibody ID 16B8

<400> 41

Gln Gln Ser Asn Ser Phe Pro Ile Thr
1 5

<210> 42

<211> 9

<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL3 Antibody ID 4C5

<400> 42

Gln Gln Ala Asp Ser Phe Pro Arg Asn
1 5

<210> 43
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL3 Antibody ID 6E7

<400> 43

Gln Gln Ala Asp Ser Phe Pro Arg Thr
1 5

<210> 44
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL3 Antibody ID 5E3

<400> 44

Gln Gln Tyr Ser Thr Tyr Pro Phe Thr
1 5

<210> 45
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL3 Antibody ID 4G10

<400> 45

Leu Gln His Asn Ser Tyr Pro Trp Thr
1 5

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 46
 <211> 115
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> VL Amino Acid Sequence Antibody ID 12G10

<400> 46

Gln Ala Val Pro Thr Gln Pro Ser Ser Leu Ser Ala Ser Pro Gly Val
 1 5 10 15

Leu Ala Ser Leu Thr Cys Thr Leu Arg Ser Gly Ile Asn Val Gly Thr
 20 25 30

Tyr Arg Ile Tyr Trp Tyr Gln Gln Lys Pro Gly Ser Pro Pro Gln Tyr
 35 40 45

Leu Leu Arg Tyr Lys Ser Asp Ser Asp Lys Gln Gln Gly Ser Gly Val
 50 55 60

Pro Ser Arg Phe Ser Gly Ser Lys Asp Ala Ser Ala Asn Ala Gly Ile
 65 70 75 80

Leu Leu Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys
 85 90 95

Met Ile Trp Tyr Ser Ser Ala Val Val Phe Gly Gly Gly Thr Lys Leu
 100 105 110

Thr Val Leu
 115

<210> 47
 <211> 106
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> VL Amino Acid Sequence Antibody ID 26A10

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<400> 47

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Val
20 25 30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Asn Thr Val Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 48

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> VL Amino Acid Sequence Antibody ID 26C10

<400> 48

Ser Phe Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Val
20 25 30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Met Leu Val Ile Tyr
35 40 45

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Gln Asp Thr Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 49
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> VL Amino Acid Sequence Antibody ID 26F2

<400> 49

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Val
20 25 30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Phe
35 40 45

Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 50
 <211> 106
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> VL Amino Acid Sequence Antibody ID 33B12

<400> 50

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
 1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Val
 20 25 30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
 35 40 45

Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
 50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
 65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Val Val
 85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 100 105

<210> 51
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> VL Amino Acid Sequence Antibody ID 24C12

<400> 51

Gly Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
 1 5 10 15

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Arg Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Val Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Asn Cys Gln Gln
85 90 95

Tyr Tyr Ile Thr Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile
100 105 110

Lys

<210> 52

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> VL Amino Acid Sequence Antibody ID 24G6

<400> 52

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys His Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Phe Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Ser Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 53
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> VL Amino Acid Sequence Antibody ID 24A10

<400> 53

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Thr Cys Lys Ser Ser His Asn Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys His Gln
85 90 95

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Tyr Tyr Ser Thr Pro Cys Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile
100 105 110

Lys

<210> 54
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> VL Amino Acid Sequence Antibody ID 10E3

<400> 54

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30

Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Val
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Phe Tyr Tyr Cys Leu Gln Asp Asn Asn Trp Pro Pro
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 55
<211> 107
<212> PRT
<213> Artificial Sequence

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<220>

<223> VL Amino Acid Sequence Antibody ID 13E7 14C12

<400> 55

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30

Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Val
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Asp Asn Asn Trp Pro Pro
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 56

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> VL Amino Acid Sequence Antibody ID 25F12

<400> 56

Glu Lys Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Asn Asn Asn
20 25 30

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 57
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> VL Amino Acid Sequence Antibody ID 25F12

<400> 57

Glu Phe Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ile Ile Ser Ser Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Ser Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Phe Asp Ser Ser Pro
85 90 95

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Ile Thr Phe Gly Arg Gly Thr Arg Leu Asp Ile Lys
100 105

<210> 58
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> VL Amino Acid Sequence Antibody ID 24F4

<400> 58

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Leu Tyr Tyr Cys Gln Gln Tyr Asp Thr Ser Pro
85 90 95

Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 59
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> VL Amino Acid Sequence Antibody ID 16B8

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<400> 59

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Val Thr Cys Arg Ala Ser Gln Asp Ile Asn Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Ser Cys Gln Gln Ser Asn Ser Phe Pro Ile
85 90 95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 60

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> VL Amino Acid Sequence Antibody ID 4C5

<400> 60

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Tyr Ala Ala Ser Ser Leu Gln Val Gly Val Pro Leu Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asp Ser Phe Pro Arg
85 90 95

Asn Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 61

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> VL Amino Acid Sequence Antibody ID 6E7

<400> 61

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Asn Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Ala Asp Ser Phe Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 62
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> VL Amino Acid Sequence Antibody ID 5E3

<400> 62

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
 20 25 30

Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
 35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Lys Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Thr Tyr Pro Phe
 85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
 100 105

<210> 63
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Exemplary Anti-Human TREM2 Antibody Light Chain Variable Region
 Amino Acid Sequences - VL Amino Acid Sequence

<400> 63

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

A-2129-W0-PCT_Sequence_Listing_ST25.txt

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1           5           10           15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
    20                25                30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Asn Ala Pro Lys Arg Leu Ile
    35                40                45

Tyr Ala Ala Ser Ser Leu Pro Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                55                60

Ser Gly Ser Gly Pro Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
    65                70                75                80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Trp
    85                90                95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Thr
    100                105

<210> 64
<211> 113
<212> PRT
<213> Homo sapiens

<400> 64

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1           5           10           15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
    20                25                30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
    35                40                45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                55                60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
    65                70                75                80

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A-2129-W0-PCT_Sequence_Listing_ST25.txt

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Ser Thr Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile
100 105 110

Lys

<210> 65
<211> 113
<212> PRT
<213> Homo sapiens

<400> 65

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Ser Thr Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile
100 105 110

Lys

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 66
 <211> 113
 <212> PRT
 <213> Homo sapiens

<400> 66

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
 1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
 20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
 35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
 50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
 85 90 95

Tyr Tyr Ser Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
 100 105 110

Lys

<210> 67
 <211> 107
 <212> PRT
 <213> Homo sapiens

<400> 67

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn

A-2129-W0-PCT_Sequence_Listing_ST25.txt

20

25

30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 68
<211> 107
<212> PRT
<213> Homo sapiens

<400> 68

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Trp
85 90 95

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 69
<211> 108
<212> PRT
<213> Homo sapiens

<400> 69

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
85 90 95

Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 70
<211> 108
<212> PRT
<213> Homo sapiens

<400> 70

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
85 90 95

Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 71
<211> 107
<212> PRT
<213> Homo sapiens

<400> 71

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Ile

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 72
<211> 107
<212> PRT
<213> Homo sapiens

<400> 72

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 73
<211> 107
<212> PRT
<213> Homo sapiens

<400> 73

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
20 25 30

Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 74
<211> 107
<212> PRT
<213> Homo sapiens

<400> 74

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 75
<211> 116
<212> PRT
<213> Homo sapiens

<400> 75

Gln Ala Val Leu Thr Gln Pro Ala Ser Leu Ser Ala Ser Pro Gly Ala
1 5 10 15

Ser Ala Ser Leu Thr Cys Thr Leu Arg Ser Gly Ile Asn Val Gly Thr
20 25 30

Tyr Arg Ile Tyr Trp Tyr Gln Gln Lys Pro Gly Ser Pro Pro Gln Tyr
35 40 45

Leu Leu Arg Tyr Lys Ser Asp Ser Asp Lys Gln Gln Gly Ser Gly Val
50 55 60

Pro Ser Arg Phe Ser Gly Ser Lys Asp Ala Ser Ala Asn Ala Gly Ile
65 70 75 80

Leu Leu Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys
85 90 95

Met Ile Trp His Ser Ser Ala Ser Val Val Phe Gly Gly Gly Thr Lys
100 105 110

Leu Thr Val Leu
115

<210> 76
<211> 107
<212> PRT
<213> Homo sapiens

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<400> 76

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Ala Val
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 77

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Exemplary Anti-Human TREM2 Antibody Heavy Chain Variable Region
Amino Acid Sequences - CDRH1

<400> 77

Ser Tyr Ala Met Ser
1 5

<210> 78

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1 Antibody ID 26A10

<400> 78

Ser Phe Gly Met Ser
1 5

<210> 79

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1 Antibody ID 24A10

<400> 79

Asn Tyr Ala Met Ser
1 5

<210> 80

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1 Antibody ID 10E3

<400> 80

Asn Tyr Trp Ile Gly
1 5

<210> 81

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1 Antibody ID 13E7 14C12

<400> 81

Ser Tyr Trp Ile Gly
1 5

<210> 82

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1 Antibody ID 25F12

<400> 82

Ser Tyr Tyr Trp Ser
1 5

<210> 83

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1 Antibody 16B8

<400> 83

Asn Tyr Gly Ile Ser
1 5

<210> 84

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1 Antibody ID 4C5

<400> 84

Asn Tyr Trp Ile Ala
1 5

<210> 85

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1 Antibody ID 6E7

<400> 85

Ser Tyr Trp Ile Ala
1 5

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 86
 <211> 5
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRH1 Antibody ID 5E3

<400> 86

Gly Tyr Tyr Ile His
 1 5

<210> 87
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRH2 Antibody ID 12G10 24C12

<400> 87

Ala Ile Gly Gly Gly Gly Val Ser Thr Tyr Cys Ala Asp Ser Val Lys
 1 5 10 15

Gly

<210> 88
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Exemplary Anti-Human TREM2 Antibody Heavy Chain Variable Region
 Amino Acid Sequences - CDRH2

<400> 88

Tyr Ile Ser Ser Ser Ser Phe Thr Ile Tyr Tyr Ala Asp Ser Val Lys
 1 5 10 15

Gly

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 89
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRH2 Antibody 26A10

<400> 89

Tyr	Ile	Ser	Lys	Ser	Ser	Phe	Thr	Ile	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 90
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRH2 Antibody ID24G6

<400> 90

Ala	Ile	Ser	Gly	Ser	Gly	Gly	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 91
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRH2 Antibody ID 10E3

<400> 91

Ile	Ile	Tyr	Pro	Gly	Asp	Ser	Asp	Thr	Arg	Tyr	Ser	Pro	Ser	Phe	Gln
1				5					10					15	

Gly

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 92
 <211> 16
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRH2 Antibody ID 25F12

<400> 92

Glu	Ile	Asn	His	Ser	Gly	Asn	Thr	Asn	Tyr	Asn	Pro	Ser	Leu	Lys	Ser
1				5				10					15		

<210> 93
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRH2 Antibody ID 16B8

<400> 93

Trp	Ile	Ser	Ala	Tyr	Asn	Gly	Asn	Thr	Asn	Tyr	Ala	Gln	Lys	Leu	Gln
1				5				10				15			

Gly

<210> 94
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRH2 Antibody 4C5

<400> 94

Trp	Ile	Asn	Pro	Tyr	Ser	Gly	Gly	Thr	Thr	Ser	Ala	Gln	Lys	Phe	Gln
1				5				10				15			

Gly

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 95

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH3 Antibody 12G10 24C12

<400> 95

Phe Tyr Ile Ala Val Ala Gly Ser His Phe Asp Tyr
1 5 10

<210> 96

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH3 Antibody ID 26A10

<400> 96

Glu Gly Gly Leu Thr Met Val Arg Gly Val Ser Ser Tyr Gly Leu Asp
1 5 10 15

Val

<210> 97

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH3 Antibody ID 26C10

<400> 97

Glu Gly Gly Ile Thr Met Val Arg Gly Val Ser Ser Tyr Gly Met Asp
1 5 10 15

Val

<210> 98

<211> 10

<212> PRT
<213> Artificial Sequence

<220>
<223> CDRH3 Antibody ID 24G6

<400> 98

Ala Tyr Thr Pro Met Ala Phe Phe Asp Tyr
1 5 10

<210> 99
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRH3 Antibody ID 24A10

<400> 99

Gly Gly Trp Glu Leu Phe Tyr
1 5

<210> 100
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRH3 Antibody ID 10E3

<400> 100

Arg Arg Gln Gly Ile Trp Gly Asp Ala Leu Asp Ile
1 5 10

<210> 101
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRH3 Antibody ID 13E7 14C12

<400> 101

Arg Arg Gln Gly Ile Trp Gly Asp Ala Leu Asp Phe
1 5 10

<210> 102
 <211> 16
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRH3 Antibody ID 25F12

<400> 102

Glu	Gly	Tyr	Tyr	Asp	Ile	Leu	Thr	Gly	Tyr	His	Asp	Ala	Phe	Asp	Ile
1				5				10						15	

<210> 103
 <211> 13
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRH3 Antibody ID 32E3

<400> 103

His	Asp	Ile	Ile	Pro	Ala	Ala	Pro	Gly	Ala	Phe	Asp	Ile
1				5				10				

<210> 104
 <211> 13
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRH3 Antibody ID 24F4

<400> 104

Gln	Ala	Ile	Ala	Val	Thr	Gly	Leu	Gly	Gly	Phe	Asp	Pro
1				5				10				

<210> 105
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRH3 Antibody ID 16B8

<400> 105

Arg Gly Tyr Ser Tyr Gly Ser Phe Asp Tyr
1 5 10

<210> 106

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH3 Antibody ID 4C5

<400> 106

Gln Arg Thr Phe Tyr Tyr Asp Ser Ser Gly Tyr Phe Asp Tyr
1 5 10

<210> 107

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH3 Antibody ID 6E7

<400> 107

Gln Arg Thr Phe Tyr Tyr Asp Ser Ser Asp Tyr Phe Asp Tyr
1 5 10

<210> 108

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH3 Antibody ID 5E3

<400> 108

Asp Gly Gly Tyr Leu Ala Leu Tyr Gly Thr Asp Val
1 5 10

<210> 109

<211> 13

<212> PRT

<213> Artificial Sequence

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<220>

<223> CDRH3 Antibody ID 4G10

<400> 109

Gln Gly Ile Glu Val Thr Gly Thr Gly Gly Leu Asp Val
1 5 10

<210> 110

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> VH Amino Acid Sequence Antibody ID 12G10 24C12

<400> 110

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Gly Gly Gly Gly Val Ser Thr Tyr Cys Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Phe Tyr Ile Ala Val Ala Gly Ser His Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 111
 <211> 126
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> VH Amino Acid Sequence Antibody ID 26A10

<400> 111

Glu Val Gln Leu Val Glu Ser Gly Gly Ala Leu Val Gln Arg Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Phe Thr Phe Ser Ser Phe
 20 25 30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Tyr Ile Ser Ser Ser Ser Phe Thr Ile Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Phe Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Glu Gly Gly Leu Thr Met Val Arg Gly Val Ser Ser Tyr Gly
 100 105 110

Leu Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> 112
 <211> 126
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> VH Amino Acid Sequence Antibody ID 26C10

<400> 112

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Glu Val Gln Leu Val Glu Ser Gly Gly Ala Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
20 25 30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Ser Ser Phe Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Phe Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Val Arg Glu Gly Gly Ile Thr Met Val Arg Gly Val Ser Ser Tyr Gly
100 105 110

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 113
<211> 126
<212> PRT
<213> Artificial Sequence

<220>
<223> VH Amino Acid Sequence Antibody ID 26F2

<400> 113

Glu Val Gln Leu Val Glu Ser Gly Gly Ala Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
20 25 30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Ser Tyr Ile Ser Ser Ser Ser Phe Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Phe Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Arg Glu Gly Gly Ile Thr Met Val Arg Gly Val Ser Ser Tyr Gly
100 105 110

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 114
<211> 126
<212> PRT
<213> Artificial Sequence

<220>
<223> VH Amino Acid Sequence Antibody ID 33B12

<400> 114

Glu Val Gln Leu Val Glu Ser Gly Gly Ala Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
20 25 30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Lys Ser Ser Phe Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Phe Tyr
65 70 75 80

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Gly Leu Thr Met Val Arg Gly Val Ser Ser Tyr Gly
100 105 110

Leu Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 115
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> VH Amino Acid Sequence Antibody ID 24G6

<400> 115

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Ala Tyr Thr Pro Met Ala Phe Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 116
 <211> 116
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> VH Amino Acid Sequence Antibody ID 24A10

<400> 116

Glu Val Gln Val Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Lys Gly Gly Trp Glu Leu Phe Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110

Thr Val Ser Ser
 115

<210> 117
 <211> 121
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> VH Amino Acid Sequence Antibody ID 10E3

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<400> 117

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Met Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys
85 90 95

Ala Arg Arg Arg Gln Gly Ile Trp Gly Asp Ala Leu Asp Ile Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 118

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> VH Amino Acid Sequence Antibody ID 13E7 14C12

<400> 118

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Met Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys
85 90 95

Ala Arg Arg Arg Gln Gly Ile Trp Gly Asp Ala Leu Asp Phe Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 119

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH Amino Acid Sequence Antibody ID 25F12

<400> 119

Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Ser Tyr
20 25 30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asn His Ser Gly Asn Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Glu Gly Tyr Tyr Asp Ile Leu Thr Gly Tyr His Asp Ala Phe Asp
100 105 110

Ile Trp Asp Gln Gly Thr Met Val Thr Val Phe Ser
115 120

<210> 120
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> VH Amino Acid Sequence Antibody ID 32E3

<400> 120

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Thr Leu Lys Ala Ser Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Arg His Asp Ile Ile Pro Ala Ala Pro Gly Ala Phe Asp Ile Trp
100 105 110

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 121
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> VH Amino Acid Sequence Antibody ID 24F4

<400> 121

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Thr Arg Gln Ala Ile Ala Val Thr Gly Leu Gly Gly Phe Asp Pro Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 122
<211> 119
<212> PRT
<213> Artificial Sequence

<220>

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<223> VH Amino Acid Sequence Antibody ID 16B8

<400> 122

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Gly Tyr Ser Tyr Gly Ser Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 123

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH Amino Acid Sequence Antibody ID 4C5

<400> 123

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly His Ser Phe Thr Asn Tyr
20 25 30

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Arg Gln Arg Thr Phe Tyr Tyr Asp Ser Ser Gly Tyr Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 124
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH Amino Acid Sequence Antibody ID 6E7

<400> 124

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys
85 90 95

Ala Arg Gln Arg Thr Phe Tyr Tyr Asp Ser Ser Asp Tyr Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 125
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> VH Amino Acid Sequence Antibody ID 5E3

<400> 125

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Leu Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Pro Tyr Ser Gly Gly Thr Thr Ser Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Ser Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Gly Tyr Leu Ala Leu Tyr Gly Thr Asp Val Trp Gly
100 105 110

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 126
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> VH Amino Acid Sequence Antibody ID 4G10

<400> 126

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Pro Ser Tyr
20 25 30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Phe
65 70 75 80

Leu Lys Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys
85 90 95

Ala Arg Gln Gly Ile Glu Val Thr Gly Thr Gly Gly Leu Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 127
<211> 125
<212> PRT
<213> Homo sapiens

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<400> 127

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Tyr Tyr Asp Tyr Val Trp Gly Ser Tyr Arg Tyr Thr Tyr Phe
100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 128

<211> 121

<212> PRT

<213> Homo sapiens

<400> 128

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Ser Tyr Ile Ser Ser Ser Ser Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Leu Thr Gly Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly
100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 129
<211> 122
<212> PRT
<213> Homo sapiens

<400> 129

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Ala Lys Ala Tyr Cys Gly Gly Asp Cys Tyr Ser Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 130
<211> 120
<212> PRT
<213> Homo sapiens

<400> 130

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Gly Thr Thr Gly Thr Ala Glu Tyr Phe Gln His Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 131
<211> 118
<212> PRT
<213> Homo sapiens

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<400> 131

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Gly Thr Thr Gly Thr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 132

<211> 118

<212> PRT

<213> Homo sapiens

<400> 132

Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
20 25 30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Gly Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Tyr Asn Trp Asn Asp Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
100 105 110

Met Val Thr Val Ser Ser
115

<210> 133
<211> 121
<212> PRT
<213> Homo sapiens

<400> 133

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Ala Arg Val Asp Ile Val Ala Thr Ile Asp Ala Phe Asp Ile Trp Gly
100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 134
<211> 121
<212> PRT
<213> Homo sapiens

<400> 134

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Val Asp Ile Val Ala Thr Ile Asn Trp Phe Asp Pro Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 135
<211> 119
<212> PRT
<213> Homo sapiens

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<400> 135

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Ser Gly Ser Tyr Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 136

<211> 119

<212> PRT

<213> Homo sapiens

<400> 136

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Tyr Ser Gly Ser Tyr Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 137
<211> 123
<212> PRT
<213> Homo sapiens

<400> 137

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Ala Arg Asp Tyr Gly Asp Tyr Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 138
<211> 125
<212> PRT
<213> Homo sapiens

<400> 138

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Val Asp Ile Val Ala Thr Ile Tyr Tyr Tyr Tyr Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 139
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL2 Consensus for 6E7 improved Affinity variants

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> X is A or G

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> X is L or R

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> X is N, K, R, L, or T

<400> 139

Xaa Ala Ser Ser Xaa Gln Xaa
1 5

<210> 140
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL3 Consensus for 6E7 improved Affinity variants

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> X is Q or G

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> X is S or R

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> X is F, L or Y

<220>
<221> MISC_FEATURE

<222> (8)..(8)
<223> X is R or H

<400> 140

Xaa Gln Ala Asp Xaa Xaa Pro Xaa Thr
1 5

<210> 141
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRH2 Consensus for 6E7 improved Affinity variants

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> X is I or T

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> X is T or V

<220>
<221> MISC_FEATURE
<222> (11)..(11)
<223> X is Y or L

<220>
<221> MISC_FEATURE
<222> (12)..(12)
<223> X is S or A

<220>
<221> MISC_FEATURE
<222> (14)..(14)
<223> X is S, G, or E

<220>
<221> MISC_FEATURE
<222> (17)..(17)
<223> X is G or D

<400> 141

Xaa Ile Tyr Pro Gly Asp Ser Asp Xaa Arg Xaa Xaa Pro Xaa Phe Gln
1 5 10 15

Xaa

<210> 142
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRH3 Consensus for 6E7 improved Affinity variants

<220>
 <221> MISC_FEATURE
 <222> (1)..(1)
 <223> X is Q, G, S, or M

<220>
 <221> MISC_FEATURE
 <222> (12)..(12)
 <223> X is F or S

<400> 142

Xaa	Arg	Thr	Phe	Tyr	Tyr	Asp	Ser	Ser	Asp	Tyr	Xaa	Asp	Tyr
1				5					10				

<210> 143
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRL2 Antibody ID V3

<400> 143

Ala	Ala	Ser	Ser	Arg	Gln	Asn
1				5		

<210> 144
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRL2 Antibody ID V24 C01

<400> 144

Ala Ala Ser Ser Leu Gln Lys
1 5

<210> 145

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL2 Antibody ID V27 C04

<400> 145

Ala Ala Ser Ser Leu Gln Arg
1 5

<210> 146

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL2 Anitbody ID V40 D05

<400> 146

Ala Ala Ser Ser Leu Gln Leu
1 5

<210> 147

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL2 Antibody ID V84 H01

<400> 147

Gly Ala Ser Ser Leu Gln Asn
1 5

<210> 148

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL3 Antibody ID V40 D05

<400> 148

Gln Gln Ala Asp Arg Phe Pro Arg Thr
1 5

<210> 149

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL3 Antibody ID V24 C01

<400> 149

Gln Gln Ala Asp Ser Phe Pro His Thr
1 5

<210> 150

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL3 Antibody ID V48 E01

<400> 150

Gln Gln Ala Asp Ser Leu Pro Arg Thr
1 5

<210> 151

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL3 Antibody ID V49 E02 V73 G02

<400> 151

Gln Gln Ala Asp Ser Tyr Pro Arg Thr
1 5

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 152
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRL3 Antibody ID V60 F01

<400> 152

Gly Gln Ala Asp Ser Phe Pro Arg Thr
 1 5

<210> 153
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> VL Amino Acid Sequence Antibody ID V3

<400> 153

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Ser Arg Gln Asn Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Ala Asp Arg Phe Pro Arg
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 154
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> VL Amino Acid Sequence Antibody ID V24 C01

<400> 154

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Ser Leu Gln Lys Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Ala Asp Ser Phe Pro His
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105

<210> 155
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> VL Amino Acid Sequence Antibody ID V27 C04

<400> 155

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
 1 5 10 15

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Arg Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Ala Asp Ser Phe Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 156

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> VL Amino Acid Sequence Antibody ID V40 D05

<400> 156

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Leu Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

A-2129-W0-PCT_Sequence_Listing_ST25.txt

65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Ala Asp Arg Phe Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 157
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> VL Amino Acid Sequence Antibody ID V48 E01

<400> 157

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Ala Asp Ser Leu Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 158
<211> 107
<212> PRT

<213> Artificial Sequence

<220>

<223> VL Amino Acid Sequence Antibody ID V49 E02 V73 G02

<400> 158

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Arg Gln Asn Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Ala Asp Ser Tyr Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 159

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> VL Amino Acid Sequence Antibody ID V52 E05

<400> 159

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Arg Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Ala Asp Arg Phe Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 160
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> VL Amino Acid Sequence Antibody ID V60 F01

<400> 160

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Arg Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Gly Gln Ala Asp Ser Phe Pro Arg

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 161
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> VL Amino Acid Sequence Antibody ID V76 G05

<400> 161

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Lys Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Arg Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Ala Asp Ser Phe Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 162
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> VL Amino Acid Sequence Antibody ID V84 H01

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<400> 162

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Ser Leu Gln Asn Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Ala Asp Ser Phe Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 163

<211> 4

<212> PRT

<213> Artificial Sequence

<220>

<223> FR1/CDRH1 border
Antibody ID 6E7

<400> 163

Tyr Ser Phe Thr
1

<210> 164

<211> 4

<212> PRT

<213> Artificial Sequence

<220>

<223> Heavy Chain Variable Region Amino Acid Sequences for Reduced
Affinity TREM2 Antibodies - FR1/CDRH1 border

<400> 164

Tyr Ser Phe Ala

1

<210> 165

<211> 4

<212> PRT

<213> Artificial Sequence

<220>

<223> FR1/CDRH1 border
Antibody ID V3 A04

<400> 165

Tyr Ser Phe Gly

1

<210> 166

<211> 4

<212> PRT

<213> Artificial Sequence

<220>

<223> FR1/CDRH1 border
Antibody ID V49 E02

<400> 166

Tyr Ser Phe Asn

1

<210> 167

<211> 4

<212> PRT

<213> Artificial Sequence

<220>

<223> FR1/CDRH1 border
Antibody ID V52 E05

<400> 167

Tyr Ser Phe Glu

1

<210> 168
 <211> 4
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> FR1/CDRH1 border
 Antibody ID V60 F01

<400> 168

Tyr His Phe Thr
 1

<210> 169
 <211> 4
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> FR1/CDRH1 border
 Antibody ID V76 G05 V84 H01

<400> 169

Tyr Gly Phe Thr
 1

<210> 170
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRH2 Antibody ID 6E7 V3 A04

<400> 170

Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe Gln
 1 5 10 15

Asp

<210> 171
 <211> 17

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH2 Antibody ID V24 C01

<400> 171

Ile	Ile	Tyr	Pro	Gly	Asp	Ser	Asp	Val	Arg	Tyr	Ser	Pro	Ser	Phe	Gln
1				5					10					15	

Gly

<210> 172

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH2 Antibody ID V27 C04

<400> 172

Ile	Ile	Tyr	Pro	Gly	Asp	Ser	Asp	Thr	Arg	Tyr	Ala	Pro	Ser	Phe	Gln
1				5					10					15	

Gly

<210> 173

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH2 Antibody ID V49 E02

<400> 173

Thr	Ile	Tyr	Pro	Gly	Asp	Ser	Asp	Thr	Arg	Leu	Ser	Pro	Ser	Phe	Gln
1				5					10					15	

Gly

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 174
 <211> 17
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> CDRH2 Antibody ID V73 G02

 <400> 174

Ile	Ile	Tyr	Pro	Gly	Asp	Ser	Asp	Thr	Arg	Tyr	Ser	Pro	Gly	Phe	Gln
1				5					10					15	

Gly

<210> 175
 <211> 17
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> CDRH2 Antibody ID V76 G05

 <400> 175

Ile	Ile	Tyr	Pro	Gly	Asp	Ser	Asp	Thr	Arg	Tyr	Ser	Pro	Glu	Phe	Gln
1				5					10					15	

Gly

<210> 176
 <211> 14
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> CDRH3 Antibody ID V3 A04

 <400> 176

Gly	Arg	Thr	Phe	Tyr	Tyr	Asp	Ser	Ser	Asp	Tyr	Phe	Asp	Tyr
1				5					10				

<210> 177
 <211> 14

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH3 Antibody ID V24 C01

<400> 177

Ser Arg Thr Phe Tyr Tyr Asp Ser Ser Asp Tyr Phe Asp Tyr
1 5 10

<210> 178

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH3 Antibody ID V60 F01

<400> 178

Gln Arg Thr Phe Tyr Tyr Asp Ser Ser Asp Tyr Ser Asp Tyr
1 5 10

<210> 179

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH3 Antibody ID V48 E01

<400> 179

Met Arg Thr Phe Tyr Tyr Asp Ser Ser Asp Tyr Phe Asp Tyr
1 5 10

<210> 180

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH Amino Acid Sequence Antibody ID V3 A04

<400> 180

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Ala Ser Tyr
20 25 30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Asp Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys
85 90 95

Ala Arg Gly Arg Thr Phe Tyr Tyr Asp Ser Ser Asp Tyr Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 181
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH Amino Acid Sequence Antibody ID V24 C01

<400> 181

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Val Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys
85 90 95

Ala Arg Ser Arg Thr Phe Tyr Tyr Asp Ser Ser Asp Tyr Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 182
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH Amino Acid Sequence Antibody ID V27 C04

<400> 182

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ala Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys
85 90 95

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Val Arg Ser Arg Thr Phe Tyr Tyr Asp Ser Ser Asp Tyr Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 183
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH Amino Acid Sequence Antibody ID V40 D05

<400> 183

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Gly Ser Tyr
20 25 30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Val Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys
85 90 95

Ala Arg Gln Arg Thr Phe Tyr Tyr Asp Ser Ser Asp Tyr Ser Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 184
 <211> 123
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> VH Amino Acid Sequence Antibody ID V48 E01

<400> 184

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Gly Ser Tyr
 20 25 30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Val Arg Tyr Ser Pro Ser Phe
 50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys
 85 90 95

Ala Arg Met Arg Thr Phe Tyr Tyr Asp Ser Ser Asp Tyr Phe Asp Tyr
 100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 185
 <211> 123
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Heavy Chain Variable Region Amino Acid Sequences for Improved
 Affinity TREM2 Antibodies - VH Amino Acid Sequence

<400> 185

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Asn Ser Tyr
20 25 30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Thr Ile Tyr Pro Gly Asp Ser Asp Thr Arg Leu Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys
85 90 95

Ala Arg Ser Arg Thr Phe Tyr Tyr Asp Ser Ser Asp Tyr Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 186
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH Amino Acid Sequence Antibody ID V49 E02

<400> 186

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Glu Ser Tyr
20 25 30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met

A-2129-W0-PCT_Sequence_Listing_ST25.txt

35

40

45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys
85 90 95

Ala Arg Gly Arg Thr Phe Tyr Tyr Asp Ser Ser Asp Tyr Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 187

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH Amino Acid Sequence Antibody ID V60 F01

<400> 187

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr His Phe Thr Ser Tyr
20 25 30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Val Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys
85 90 95

Ala Arg Gln Arg Thr Phe Tyr Tyr Asp Ser Ser Asp Tyr Ser Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 188
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH Amino Acid Sequence Antibody ID V73 G02

<400> 188

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Gly Ser Tyr
20 25 30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Gly Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys
85 90 95

Ala Arg Gly Arg Thr Phe Tyr Tyr Asp Ser Ser Asp Tyr Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser

A-2129-W0-PCT_Sequence_Listing_ST25.txt

115

120

<210> 189
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH Amino Acid Sequence Antibody ID V76 G05

<400> 189

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Gly Ser Tyr
20 25 30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Glu Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys
85 90 95

Ala Arg Gln Arg Thr Phe Tyr Tyr Asp Ser Ser Asp Tyr Ser Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 190
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH Amino Acid Sequence Antibody ID V84 H01

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<400> 190

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Gly Phe Thr Ser Tyr
20 25 30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys
85 90 95

Ala Arg Gln Arg Thr Phe Tyr Tyr Asp Ser Ser Asp Tyr Ser Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 191

<211> 106

<212> PRT

<213> Homo sapiens

<400> 191

Gly Gln Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser
1 5 10 15

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
20 25 30

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro
35 40 45

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Val Lys Ala Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn
50 55 60

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65 70 75 80

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
85 90 95

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
100 105

<210> 192
<211> 106
<212> PRT
<213> Homo sapiens

<400> 192

Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
1 5 10 15

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
20 25 30

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
35 40 45

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
50 55 60

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65 70 75 80

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
85 90 95

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
100 105

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 193
 <211> 105
 <212> PRT
 <213> Homo sapiens

<400> 193

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
 1 5 10 15

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
 20 25 30

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
 35 40 45

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
 50 55 60

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
 65 70 75 80

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
 85 90 95

Lys Thr Val Ala Pro Thr Glu Cys Ser
 100 105

<210> 194
 <211> 106
 <212> PRT
 <213> Homo sapiens

<400> 194

Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
 1 5 10 15

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
 20 25 30

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro

A-2129-W0-PCT_Sequence_Listing_ST25.txt

35

40

45

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
50 55 60

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65 70 75 80

Ser His Lys Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
85 90 95

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
100 105

<210> 195
<211> 106
<212> PRT
<213> Homo sapiens

<400> 195

Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
1 5 10 15

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Val Ser Asp
20 25 30

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro
35 40 45

Val Lys Val Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn
50 55 60

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65 70 75 80

Ser His Arg Ser Tyr Ser Cys Arg Val Thr His Glu Gly Ser Thr Val
85 90 95

Glu Lys Thr Val Ala Pro Ala Glu Cys Ser
100 105

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 196
 <211> 106
 <212> PRT
 <213> Homo sapiens

<400> 196

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1 5 10 15

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
 20 25 30

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35 40 45

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50 55 60

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65 70 75 80

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85 90 95

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 100 105

<210> 197
 <211> 107
 <212> PRT
 <213> Homo sapiens

<400> 197

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
 1 5 10 15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
 20 25 30

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
35 40 45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65 70 75 80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
85 90 95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 198
<211> 330
<212> PRT
<213> Homo sapiens

<400> 198

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys

A-2129-W0-PCT_Sequence_Listing_ST25.txt

100

105

110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr

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<210> 199
<211> 330
<212> PRT
<213> Homo sapiens
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<400> 199

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 200

<211> 330

<212> PRT

<213> Homo sapiens

<400> 200

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 201
<211> 330
<212> PRT
<213> Homo sapiens

<400> 201

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 202
<211> 330
<212> PRT
<213> Homo sapiens

<400> 202

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys

A-2129-W0-PCT_Sequence_Listing_ST25.txt

100

105

110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr

A-2129-W0-PCT_Sequence_Listing_ST25.txt

305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 203
<211> 330
<212> PRT
<213> Homo sapiens

<400> 203

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 204

<211> 326

<212> PRT

<213> Homo sapiens

<400> 204

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	1	5	10	15
Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	20	25	30	
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	35	40	45	
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	50	55	60	
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Asn	Phe	Gly	Thr	Gln	Thr	65	70	75	80
Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	85	90	95	
Thr	Val	Glu	Arg	Lys	Cys	Cys	Val	Glu	Cys	Pro	Pro	Cys	Pro	Ala	Pro	100	105	110	
Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	115	120	125	
Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	130	135	140	
Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	145	150	155	160
Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	165	170	175	
Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Val	His	Gln	Asp	Trp	180	185	190	
Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	195	200	205	

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
210 215 220

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
225 230 235 240

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
245 250 255

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
260 265 270

Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
275 280 285

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
290 295 300

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
305 310 315 320

Ser Leu Ser Pro Gly Lys
325

<210> 205
<211> 330
<212> PRT
<213> Homo sapiens

<400> 205

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 206
<211> 12
<212> PRT
<213> Homo sapiens

<400> 206

Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro
1 5 10

<210> 207
<211> 110
<212> PRT
<213> Homo sapiens

<400> 207

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
65 70 75 80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro
100 105 110

<210> 208
<211> 345
<212> DNA
<213> Artificial Sequence

<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
12G10

<400> 208
caggctgtgc cgactcagcc gtcttcctc tctgcatctc ctggagtatt agccagtctc 60
acctgcacct tacgcagtgg catcaatgtt ggtacctaca ggatatactg gtaccagcag 120
aagccaggga gtcctcccca gtatctcctg aggtacaaat cagactcaga taagcagcag 180
ggctctggag tccccagccg cttctctgga tccaaggatg cttcggccaa tgcagggatt 240
ttactcatct ctgggctcca gtctgaggat gaggctgact attactgtat gatttggtac 300
agcagtgtcg tggtattcgg cggagggacc aaactgaccg tccta 345

<210> 209
<211> 318
<212> DNA
<213> Artificial Sequence

<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
26A10

<400> 209
tcctatgagc tgactcagcc accctcagtg tccgtgtccc caggacagac agccagcatc 60
acctgctctg gagataaatt gggagataag tatgtttgct ggtatcagca gaagccaggc 120
cagtcccctg tgctggatcat ctatcaagat agcaagcggc cctcagggat ccctgagcga 180

A-2129-W0-PCT_Sequence_Listing_ST25.txt

ttctctggct ccaactctgg gaacacagcc actctgacca tcagcgggac ccaggctatg	240
gatgaggctg actattactg tcaggcgtgg gacagtaaca ctgtggtatt cggcggaggg	300
accaagctga ccgtccta	318

<210> 210
 <211> 318
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID 26C10

<400> 210	
tcctttgagc tgactcagcc accctcagtg tccgtgtccc caggacagac agccagcatc	60
acctgctctg gagataaatt gggggataag tatgtttgct ggtatcagca gaagccaggc	120
cagtccccta tgttggtcat ctatcaagat accaagcggc cctcagggat ccctgaacga	180
ttctctggct ccaactctgg gaacacagcc actctgacca tcagcgggac ccaggctatg	240
gatgaggctg actattactg tcaggcgtgg gacagcagca ctgtggtctt cggcggaggg	300
accaagctga ccgtccta	318

<210> 211
 <211> 318
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID 26F2

<400> 211	
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acctgctctg gagataaatt gggggataag tatgtttgct ggtatcagca gaagccaggc	120
cagtcccctg tgttggtcat ctttcaagat agcaagcggc cctcagggat ccctgagcga	180
ttctctggct ccaactctgg gaacacagcc actctgacca tcagcgggac ccaggctatg	240
gatgaggctg actattactg tcaggcgtgg gacagcagca ctgtggtatt cggcggaggg	300
accaagctga ccgtccta	318

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 212
<211> 318
<212> DNA
<213> Artificial Sequence

<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
33B12

<400> 212
tcctatgagc tgactcagcc accctcagtg tccgtgtccc caggacagac agccagcatc 60
acctgctctg gagataaatt gggggataag tatgttttgct ggtatcagca gaagccaggc 120
cagtcccctg tgttggtcat ctatcaagat agcaagcggc cctcagggat ccctgagcga 180
ttctctggct ccaactctgg gaacacagcc actctgacca tcagcgggac ccaggctatg 240
gatgaggctg actattactg tcaggcgtgg gacagtagca ctgtggtatt cggcggaggg 300
accaagctga ccgtccta 318

<210> 213
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
24C12

<400> 213
ggcatcgtga tgaccagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc 60
atcaactgca agtccagccg gagtgttttg tacagctcca acaataagaa ctacttagct 120
tggtaccagc agaaaccagg acagcctcct aagggtgtca ttactgggc atctaccgg 180
gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240
atcagcagcc tgcaggctga agatgtggca gtttataact gtcagcaata ttatattact 300
ccgatcacct tcggccaagg gacacgactg gagattaa 339

<210> 214
<211> 339
<212> PRT
<213> Artificial Sequence

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<220>

<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
24G6

<400> 214

Gly Ala Cys Ala Thr Cys Gly Thr Gly Ala Thr Gly Ala Cys Cys Cys
1 5 10 15

Ala Gly Thr Cys Thr Cys Cys Ala Gly Ala Cys Thr Cys Cys Cys Thr
20 25 30

Gly Gly Cys Thr Gly Thr Gly Thr Cys Thr Cys Thr Gly Gly Gly Cys
35 40 45

Gly Ala Gly Ala Gly Gly Gly Cys Cys Ala Cys Cys Ala Thr Cys Ala
50 55 60

Ala Cys Thr Gly Cys Ala Ala Gly Thr Cys Cys Ala Gly Cys Cys Ala
65 70 75 80

Gly Ala Gly Thr Gly Thr Thr Thr Thr Ala Thr Ala Cys Ala Gly Cys
85 90 95

Thr Cys Cys Ala Ala Cys Ala Ala Thr Ala Ala Gly Cys Ala Cys Thr
100 105 110

Thr Cys Thr Thr Ala Gly Cys Thr Thr Gly Gly Thr Ala Cys Cys Ala
115 120 125

Gly Cys Ala Gly Ala Ala Ala Cys Cys Ala Gly Gly Ala Cys Ala Gly
130 135 140

Cys Cys Thr Cys Cys Thr Ala Ala Gly Cys Thr Gly Cys Thr Cys Ala
145 150 155 160

Thr Thr Thr Ala Cys Thr Gly Gly Gly Cys Ala Thr Cys Thr Ala Cys
165 170 175

Cys Cys Gly Gly Gly Ala Gly Thr Cys Cys Gly Gly Gly Gly Thr Cys

A-2129-W0-PCT_Sequence_Listing_ST25.txt

180

185

190

Cys Cys Thr Gly Ala Cys Cys Gly Ala Thr Thr Cys Ala Gly Thr Gly
195 200 205

Gly Cys Ala Gly Cys Gly Gly Gly Thr Cys Thr Gly Gly Gly Ala Cys
210 215 220

Ala Gly Ala Thr Thr Thr Cys Ala Cys Thr Cys Thr Cys Ala Cys Cys
225 230 235 240

Ala Thr Cys Ala Gly Cys Ala Gly Cys Cys Thr Gly Cys Ala Gly Gly
245 250 255

Cys Thr Gly Ala Ala Gly Ala Thr Gly Thr Gly Gly Cys Ala Thr Thr
260 265 270

Thr Thr Ala Thr Thr Ala Cys Thr Gly Thr Cys Ala Gly Cys Ala Ala
275 280 285

Thr Ala Thr Thr Ala Thr Ala Gly Thr Ala Cys Thr Cys Cys Gly Cys
290 295 300

Thr Cys Ala Cys Thr Thr Thr Cys Gly Gly Cys Gly Gly Ala Gly Gly
305 310 315 320

Gly Ala Cys Cys Ala Ala Gly Gly Thr Gly Gly Ala Gly Ala Thr Cys
325 330 335

Ala Ala Ala

<210> 215

<211> 339

<212> DNA

<213> Artificial Sequence

<220>

<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody
24A10

A-2129-W0-PCT_Sequence_Listing_ST25.txt

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<400> 215
gacatcgtga tgaccagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc      60
atcacctgca agtccagcca caatgtttta tacagctcca acaataagaa ctacttagct      120
tggtatcagc agaaaccagg acagcctcct aaactgctca tttactgggc atctaccgg      180
gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc      240
atcagcagcc tgcaggctga agatgtggca gtttattact gtcaccaata ttatagtact      300
ccgtgcagtt ttggccaggg gaccaagctg gagatcaaa      339
```

```
<210> 216
<211> 321
<212> DNA
<213> Artificial Sequence
```

```
<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
      10E3
```

```
<400> 216
gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc      60
ctctcctgca gggccagtca gagtgtttagc agcaacttag cctggttcca gcagaaacct      120
ggccaggctc ccaggctcct catctatggt gcttccacca gggccactgg tattccagcc      180
aggttcagtg tcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct      240
gaagattttg cattttatta ctgtctgcag gataataatt ggccctccac tttcggccct      300
gggaccaaag tggatatcaa a      321
```

```
<210> 217
<211> 321
<212> DNA
<213> Artificial Sequence
```

```
<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
      13E7
```

```
<400> 217
gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc      60
ctctcctgca gggccagtca gagtgtttagc agcaacttag cctggttcca gcagaaacct      120
ggccaggctc ccaggctcct catctatggt gcttccacca gggccactgg tattccagcc      180
```

A-2129-W0-PCT_Sequence_Listing_ST25.txt

aggttcagtgc	tcagtgggtc	tgggacagag	ttcactctca	ccatcagcag	cctgcagtct	240
gaagattttg	cagtttatta	ctgtctgcag	gataataatt	ggcctccac	tttcggccct	300
gggaccaaag	tggatatcaa	a				321

<210> 218
 <211> 321
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID 25F12

<400> 218	
gaaaaagtga	tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
ctctcctgca	gggccagtcagtagtggttaac aacaacttag cctgggtacca gcagaaacct 120
ggccaggctc	ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc 180
aggttcagtgc	gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240
gaagattttg	cagtttatta ctgtcagcag tataataact ggcctcggac gttcggccaa 300
gggaccaagg	tggaaatcaa a 321

<210> 219
 <211> 324
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID 32E3

<400> 219	
gaatttgtgt	tgacgcagtc tccaggcacc ctgtctttgt ctccggggga aagagccacc 60
ctctcctgca	gggccagtcagtagtattagc agcaactact tagcctggta ccagcagaaa 120
cctggccagg	ctcccaggct cctcatctat agtgcaccca gcagggccac tggcatccca 180
gacaggttca	gtggcagtggt gtctgggaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt	ttgcagtgtg ttactgtcag cagtttgata gctcaccgat caccttcggc 300
cgagggacac	gactggacat taaa 324

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 220
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
24F4

<400> 220
gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcagctact tagcctggta ccagcagaaa 120
cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt ttgactgta ttactgtcag cagtatgata cctcaccatt cactttcggc 300
cctgggacca aagtggatat caaa 324

<210> 221
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
16B8

<400> 221
gacatccaga tgaccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
gtcacttgtc gggcgagtca ggatattaac agctgggttag cctgggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatcctctt tgcaaactgg ggtcccttca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttactc ttgtcaacag tctaacagtt tcccgatcac cttcggccaa 300
gggacacgac tggagattaa a 321

<210> 222
<211> 321
<212> DNA
<213> Artificial Sequence

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<220>

<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID 4C5

<400> 222

gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc	60
atcacttgtc gggcgagtca ggggtattagc aactgggtag cctgggtatca gcagaaacca	120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaagttgg ggtcccatta	180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct	240
gaagattttg caacttacta ttgtcaacag gctgacagtt tccctcgcaa ttttggccag	300
gggaccaagc tggagatcaa a	321

<210> 223

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID 6E7 V9 A10 V30 C07 V33 C10 V44 D09 V68 F09

<400> 223

gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc	60
atcacttgtc gggcgagtca ggggtattagc agctgggtag cctgggtatca gcagaaacca	120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaaatgg ggtcccatta	180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct	240
gaagattttg caacttactt ttgtcaacag gctgacagtt tccctcgcac ttttggccag	300
gggaccaagc tggagatcaa a	321

<210> 224

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV - Antibody ID 5E3

<400> 224

A-2129-W0-PCT_Sequence_Listing_ST25.txt

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gacatccaga tgaccagtc tccatcctca ctgtctgcat ctgtaggaga cagagtcacc      60
atcacttgtc gggcgagtca gggcattagc aattatttag cctgggttca gcagaaacca      120
gggaaagccc ctaaatccct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca      180
aagttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct      240
gaagattttg caacttatta ctgccaacag tatagtactt acccattcac tttcggccct      300
gggaccaaag tggatatcaa a                                              321

```

<210> 225
 <211> 321
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID 4G10

```

<400> 225
gacatccaga tgaccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc      60
atcacttgcc gggcaagtca gggcataaga aatgatttag gctgggtatca gcagaaacca      120
gggaatgccc ctaagcgctt gatctatgct gcatccagtt tgccaagtgg ggtcccatca      180
aggttcagcg gcagtggatc tgggccagaa ttcactctca caatcagcag tctgcagcct      240
gaagattttg caacttatta ctgtctacag cataatagtt acccgtggac gttcggccaa      300
gggaccaagg tggaaatcac a                                              321

```

<210> 226
 <211> 321
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID V3 A04

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<400> 226
gacatccaga tgaccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc      60
atcacttgtc gggcgagtca ggggtattag agctgggttag cctgggtatca gcagaaacca      120
gggaaagccc ctaagctcct gatctatgct gcatccagta ggcaaaatgg ggtcccatca      180

```

A-2129-W0-PCT_Sequence_Listing_ST25.txt

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct	240
gaagattttg caacttactt ttgtcaacag gctgacaggt tccctcgacac ttttggccag	300
gggaccaagc tggagatcaa a	321

<210> 227
 <211> 321
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
 V24 C01

<400> 227	
gacatccaga tgaccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc	60
atcacttgct gggcgagtca ggggtattagc agctgggttag cctgggtatca gcagaaacca	120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaaagg ggtcccatca	180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct	240
gaagattttg caacttactt ttgtcaacag gctgacagtt tccctcatac ttttggccag	300
gggaccaagc tggagatcaa a	321

<210> 228
 <211> 321
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
 V27

<400> 228	
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atcacttgct gggcgagtca ggggtattagc agctgggttag cctgggtatca gcagaaacca	120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaacgtgg ggtcccatca	180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct	240
gaagattttg caacttactt ttgtcaacag gctgacagtt tccctcgacac ttttggccag	300
gggaccaagc tggagatcaa a	321

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 229
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
V40 D05

<400> 229
gacatccaga tgaccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgct gggcgagtca ggggtattagc agctggtttag cctgggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaacttgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttactt ttgtcaacag gctgaccgtt tccctcgcac ttttggccag 300
gggaccaagc tggagatcaa a 321

<210> 230
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
V48 E01

<400> 230
gacatccaga tgaccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgct gggcgagtca ggggtattagc agctggtttag cctgggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaacggg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttactt ttgtcaacag gctgacagtt tgcctcgcac ttttggccag 300
gggaccaagc tggagatcaa a 321

<210> 231
<211> 321
<212> DNA
<213> Artificial Sequence

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<220>

<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
V49 E02

<400> 231

gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc	60
atcacttgtc gggcgagtca ggggtattagc agctgggtag cctgggtatca gcagaaacca	120
gggaaagccc ctaagctcct gatctatgct gcatccagtc ggcaaaatgg ggtcccatca	180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct	240
gaagattttg caacttactt ttgtcaacag gctgacagtt atcctcgcac ttttggccag	300
gggaccaagc tggagatcaa a	321

<210> 232

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
V52 E05

<400> 232

gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc	60
atcacttgtc gggcgagtca ggggtattagc agctgggtag cctgggtatca gcagaaacca	120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagggg ggtcccatca	180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct	240
gaagattttg caacttactt ttgtcaacag gctgaccgtt tccctcgcac ttttggccag	300
gggaccaagc tggagatcaa a	321

<210> 233

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
V60 F01

<400> 233

gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc	60
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A-2129-W0-PCT_Sequence_Listing_ST25.txt

```
atcacttgtc gggcgagtca ggggtattagc agctgggtag cctgggatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagggg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttactt ttgtgggcag gctgacagtt tccctcgcac ttttggccag 300
gggaccaagc tggagatcaa a 321
```

<210> 234
 <211> 321
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
 V73 G02

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<400> 234
gacatccaga tgaccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca ggggtattagc agctgggtag cctgggatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtc gtcaaaatgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttactt ttgtcaacag gctgacagtt atcctcgcac ttttggccag 300
gggaccaagc tggagatcaa a 321
```

<210> 235
 <211> 321
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
 V76 G05

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<400> 235
gacatccaga tgaccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca ggggtattagc agctgggtag cctgggatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagggg ggtcccatca 180
aggttcagcg gcagtggatc tgggagagat ttcactctca ccatcagcag cctgcagcct 240
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A-2129-W0-PCT_Sequence_Listing_ST25.txt

gaagattttg caacttactt ttgtcaacag gctgacagtt tccctcgcac ttttggccag 300
gggaccaagc tggagatcaa a 321

<210> 236
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
V84 H01

<400> 236
gacatccaga tgaccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca ggggtattagc agctgggttag cctgggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatggt gcatccagtt tgcaaaatgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttactt ttgtcaacag gctgacagtt tcccgcgcac ttttggccag 300
gggaccaagc tggagatcaa a 321

<210> 237
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
12G10

24C12

<400> 237
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt caccttttagc agctatgccca tgagctgggt ccgccaggct 120
ccaggggaagg ggctggagtg ggtctcagct attgggtggtg gtggtggttag cacatactgc 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa tacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaattttat 300
atagcagtgg ctggttctca ctttgactac tggggccagg gaaccctggt caccgtctcc 360

tca 363

<210> 238
 <211> 378
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID 26A10

<400> 238
 gaggtgcaac tgggtggagtc tggggggagcc ttggtacagc gggggggggtc cctgagactc 60
 tcctgtgcag cctctagatt caccttcagt agctttggca tgagctgggt ccgccaggct 120
 ccagggaagg ggctggagtg ggtttcatac attagtagta gtagttttac catatattac 180
 gcagactctg tgaagggccg attcaccatc tccagagaca atgccaagaa ttcattctat 240
 ctgcaaatac acagcctgag agacgaggac acggctgtgt attactgtgc gagagagggg 300
 ggtcttacta tggttcgggg agtctcttcc tacggtttgg acgtctgggg ccaagggacc 360
 acggtcaccg tctcctca 378

<210> 239
 <211> 378
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV 26C10

<400> 239
 gaggtgcaac tgggtggagtc tggggggagcc ttggtacagc ctgggggggtc cctgagactc 60
 tcctgtgcag cctctggatt caccttcagt agctttggca tgagctgggt ccgccaggct 120
 ccagggaagg ggctggagtg ggtttcatac attagtagta gtagttttac catatactac 180
 gcagactctg tgaagggccg attcaccatc tccagagaca atgccaagaa ttcgttctat 240
 ctgcaaatac acagcctgag agacgaggac acggctgtgt atttctgtgt gagagagggg 300
 ggtataacta tggttcgggg agtctcttcc tacggtatgg acgtctgggg ccaagggacc 360
 acggtcaccg tctcctca 378

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 240
 <211> 378
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
 26F2

<400> 240
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 tcctgtgcag cctctggatt caccttcagt agctttggca tgagctgggt ccgccaggct 120
 ccagggaagg ggctggagtg gatttcatac attagtagta gtagttttac catatactac 180
 gcagactctg tgaagggccg attcaccatc tccagagaca atgccaagaa ttcattctat 240
 ctgcaaatga acagcctgag agacgaggac acggctgtgt atttctgtgc gagagagggg 300
 ggtattacta tggttcgggg agtctcttcc tacggtatgg acgtctgggg ccaagggacc 360
 acggtcaccg tctcctca 378

<210> 241
 <211> 378
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
 33B12

<400> 241
 gaggtgcaac tggtggagtc tgggggagcc ttggtacagc ctgggggggtc cctgagactc 60
 tcctgtgcag cctctggatt caccttcagt agctttggca tgagctgggt ccgccaggct 120
 ccagggaagg gcctggagtg ggtttcatac attagtaaaa gtagttttac catatactac 180
 gcagactctg tgaagggccg attcaccatc tccagagaca atgccaagaa ttcattctat 240
 ctgcaaatga acagcctgag agacgaggac acggctgtgt attactgtgc gagagagggg 300
 ggtcttacta tggttcgggg agtctcttcc tacggtttgg acgtctgggg ccaagggacc 360
 acggtcaccg tctcctca 378

<210> 242

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<211> 357
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
 24G6

<400> 242
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 tcctgtgcag cctctggatt cacctttagc agctatgcca tgagctgggt ccgccaggct 120
 ccagggaagg gactggagtg ggtctcagct attagtggta gtggtggtag cacatactac 180
 gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
 ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaggcgtat 300
 acacctatgg cattctttga ctactggggc cagggaaccc tggtcaccgt ctcctca 357

<210> 243
 <211> 348
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
 24A10

<400> 243
 gaggtgcagg tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgagactc 60
 tcctgtgcag cctctggatt cacctttagc aactatgcca tgagctgggt ccgccaggct 120
 ccagggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac 180
 gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
 ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaaggaggg 300
 tgggagctat ttactgggg ccagggaacc ctggtcaccg tctcctca 348

<210> 244
 <211> 363
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID

A-2129-W0-PCT_Sequence_Listing_ST25.txt

10E3

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<400> 244
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgatgatc      60
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cccgggaaag gcctggagtg gatggggatc atctatcctg gagactctga taccagatac      180
agcccgctcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac      240
ctgcagtgga gcagcctgaa ggcctcggac accgccatgt atttctgtgc gagacggaga      300
caggggatct ggggtgatgc tcttgatata tggggccaag ggacattggt caccgtctct      360
tca                                                                    363
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```
<210> 245
<211> 363
<212> DNA
<213> Artificial Sequence
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<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
13E7
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<400> 245
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cccgggaaag gcctggagtg gatggggatc atctatcctg gagactctga taccagatac      180
agcccgctcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac      240
ctgcagtgga gcagcctgaa ggcctcggac accgccatgt atttctgtgc gagacggaga      300
caggggatct ggggtgatgc tcttgatttc tggggccaag ggacattggt caccgtctct      360
tca                                                                    363
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<210> 246
<211> 372
<212> DNA
<213> Artificial Sequence
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<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
25F12
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A-2129-W0-PCT_Sequence_Listing_ST25.txt

<220>

<221> misc_feature

<222> (366)..(366)

<223> n is a, c, g, or t

<400> 246

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acctgcgctg tctatggtgg gtccttcagt agttactact ggagctggat ccgccagccc	120
ccagggaagg ggctggagtg gattggggaa atcaatcata gtggaaacac caactacaac	180
ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg	240
aagctgagct ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag agaggggtat	300
tacgatatct tgactgggta tcatgatgct tttgatattt gggaccaagg gacaatggtc	360
accgtntttt ca	372

<210> 247

<211> 366

<212> DNA

<213> Artificial Sequence

<220>

<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
32E3

<400> 247

gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc	60
tcctgtaagg gttctggata cagctttacc agctactgga tcggctgggt gcgccagatg	120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac	180
agcccgctcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac	240
ctgcagtgga gcaccctgaa ggcctcggac accgccatat attactgtgc gcgacatgac	300
attataccag cagcccctgg tgcttttgat atctggggcc aagggacaat ggtcaccgtc	360
tcttca	366

<210> 248

<211> 366

<212> DNA

<213> Artificial Sequence

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<220>

<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
24F4

<400> 248

gaggtgcagc	tggtgcagtc	tgagcagag	gtgaaaaagc	ccggggagtc	tctgaagatc	60
tcctgtaagg	gttctggata	cacctttacc	agctactgga	tcggctgggt	gcgccagatg	120
cccgggaaag	gcctggagtg	gatggggatc	atctatcctg	gtgactctga	taccagatac	180
agcccgtcct	tccaaggcca	ggtcaccatc	tcagtcgaca	agtccagcag	caccgcctac	240
ctgcagtgga	gcagcctgaa	ggcctcggac	accgccatat	attactgtac	gagacaggcc	300
atagcagtga	ctggtttggg	gggttttcgac	ccctggggcc	agggaaccct	ggtcaccgtc	360
tcctca						366

<210> 249

<211> 357

<212> DNA

<213> Artificial Sequence

<220>

<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
16B8

<400> 249

caggttcagc	tggtgcagtc	tgagctgag	gtgaagaagc	ctggggcctc	agtgaaggtc	60
tcctgcaagg	cttctggtta	cacctttacc	aactatggta	tcagctgggt	gcgacaggcc	120
cctggacaag	ggcttgagtg	gatgggatgg	atcagcgctt	acaatggtaa	cacaaactat	180
gcacagaagc	tccagggcag	agtcaccatg	accacagaca	catccacgag	tacagtctac	240
atggagctga	ggagcctgag	atctgacgac	acggccgtgt	attactgtgc	gagacgggga	300
tacagctatg	gttcctttga	ctactggggc	cagggaaccc	tggtcaccgt	ctcctca	357

<210> 250

<211> 369

<212> DNA

<213> Artificial Sequence

<220>

<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
4C5

A-2129-W0-PCT_Sequence_Listing_ST25.txt

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gaggtgcagc tgggtgcagtc tggagcagaa gtgaaaaagc ccggggagtc tctgaagatc      60
tcctgtaagg gttctggaca cagttttacc aactactgga tcgcctgggt gcgccagatg      120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac      180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac      240
ctgcagtgga gcagcctgaa ggcctcggac accgccgtgt atttctgtgc gagacaaagg      300
acgttttact atgatagtag tggttatatt gactactggg gccagggaac cctggtcacc      360
gtctcctca                                     369
```

```
<210> 251
<211> 369
<212> DNA
<213> Artificial Sequence
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```
<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
6E7
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<400> 251
gaggtgcagc tgggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc      60
tcctgtaagg gttctggata cagttttacc agctactgga tcgcctgggt gcgccagatg      120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac      180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac      240
ctacagtgga gcagcctgaa ggcctcggac accgccatgt atttctgtgc gagacaaagg      300
acgttttatt atgatagtag tgattatatt gactactggg gccagggaac cctggtcacc      360
gtctcctca                                     369
```

```
<210> 252
<211> 363
<212> DNA
<213> Artificial Sequence
```

```
<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
5E3
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<400> 252
caggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc      60
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A-2129-W0-PCT_Sequence_Listing_ST25.txt

tcctgcaagg cttctggata caccttcacc ggctactata tacactgggt gcgacaggcc	120
cctggactag ggcttgagt gatgggatgg atcaaccctt acagtgggtg cacaacctct	180
gcacagaagt ttcagggcag ggtcaccatg accagggaca cgtccatcag ctgagcctac	240
atggaactga gcaggctgag atctgacgac acggccgtgt attactgtgc gagagatgga	300
ggctacctgg ccctctacgg tacggacgtc tggggccaag ggaccacggt caccgtctcc	360
tca	363

<210> 253
 <211> 366
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
 4G10

<400> 253	
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tcctgtaagg gttctggata cagctttccc agctactgga tcgcctgggt gcgccagatg	120
cccgggaaag gcctggagt gatggggatc atctatcctg gtgactctga taccagatac	180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgccttt	240
ttgaagtgga gtagcctgaa ggcctcggac accgcatgt atttctgtgc gcgacagggt	300
atagaagtga ctggtacggg aggtttggac gtctggggcc aaggggaccac ggtcaccgtc	360
tcctca	366

<210> 254
 <211> 369
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
 V3 A04

<400> 254	
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tcctgtaagg gttctggata cagttttgcg agctactgga tcgcctgggt gcgccagatg	120

A-2129-W0-PCT_Sequence_Listing_ST25.txt

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cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac      180
agcccgtcct tccaagatca ggtcaccatc tcagccgaca agtccatcag caccgcctac      240
ctacagtgga gcagcctgaa ggcctcggac accgccatgt atttctgtgc gagagggagg      300
acgttttatt atgatagtag tgattatfff gactactggg gccaggggaa cctggtcacc      360
gtgtcctca                                     369

```

<210> 255
 <211> 369
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
 V24 C01

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<400> 255
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tcctgtaagg gttctggata cagttttacc agctactgga ttgcctgggt gcgccagatg      120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga tgtgagatac      180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac      240
ctacagtgga gcagcctgaa ggcctcggac accgccatgt atttctgtgc gagatctagg      300
acgttttatt atgatagtag tgattatfff gactactggg gccaggggaa cctggtcacc      360
gtgtcctca                                     369

```

<210> 256
 <211> 369
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
 V27 C04

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<400> 256
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc      60
tcctgtaagg gttctggata cagttttacc agctactgga tcgcctgggt gcgccagatg      120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac      180

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A-2129-W0-PCT_Sequence_Listing_ST25.txt

gctccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac	240
ctacagtgga gcagcctgaa ggcctcggac accgccatgt atttctgtgt gagaagtagg	300
acgttttatt atgatagtag tgattatatt gactactggg gccagggaac cctggtcacc	360
gtgtcctca	369

<210> 257
 <211> 369
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
 V40 D05

<400> 257	
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tcctgtaagg gttctggata cagttttggg agctactgga tcgcctgggt gcgccagatg	120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga tgtagatac	180
agcccgctcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac	240
ctacagtgga gcagcctgaa ggcctcggac accgccatgt atttctgtgc gagacaaagg	300
acgttttatt atgatagtag tgattattcg gactactggg gccagggaac cctggtcacc	360
gtgtcctca	369

<210> 258
 <211> 369
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
 V48 E01

<400> 258	
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tcctgtaagg gttctggata cagttttggt agctactgga tcgcctgggt gcgccagatg	120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga tgtgagatac	180
agcccgctcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac	240

A-2129-W0-PCT_Sequence_Listing_ST25.txt

ctacagtgga gcagcctgaa ggcctcggac accgccatgt atttctgtgc gagaatgagg	300
acgttttatt atgatagtag tgattatattt gactactggg gccagggaac cctggtcacc	360
gtgtcctca	369

<210> 259
 <211> 369
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
 V49 E02

<400> 259	
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tcctgtaagg gttctggata cagttttaat agctactgga tcgcctgggt gcgccagatg	120
cccgggaaag gcctggagtg gatggggacg atctatcctg gtgactctga taccagactg	180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac	240
ctacagtgga gcagcctgaa ggcctcggac accgccatgt atttctgtgc gagaagtagg	300
acgttttatt atgatagtag tgattatattt gactactggg gccagggaac cctggtcacc	360
gtgtcctca	369

<210> 260
 <211> 369
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
 V52 E05

<400> 260	
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tcctgtaagg gttctggata cagttttgag agctactgga tcgcctgggt gcgccagatg	120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac	180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac	240
ctacagtgga gcagcctgaa ggcctcggac accgccatgt atttctgtgc gagagggagg	300

A-2129-W0-PCT_Sequence_Listing_ST25.txt

acgtttttatt atgatagtag tgattatattt gactactggg gccagggaac cctggtcacc 360
gtgtcctca 369

<210> 261
<211> 369
<212> DNA
<213> Artificial Sequence

<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
V60 F01

<400> 261
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tcctgtaagg gttctggata ccattttacc agctactgga tcgcctgggt gcgccagatg 120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga tgtgagatac 180
agcccgctcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac 240
ctacagtgga gcagcctgaa ggcctcggac accgccatgt atttctgtgc gagacaaagg 300
acgtttttatt atgatagtag tgattatagt gactactggg gccagggaac cctggtcacc 360
gtgtcctca 369

<210> 262
<211> 369
<212> DNA
<213> Artificial Sequence

<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
V73 G02

<400> 262
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tcctgtaagg gttctggata cagttttggt agctactgga tcgcctgggt gcgccagatg 120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac 180
agcccggggt tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac 240
ctacagtgga gcagcctgaa ggcctcggac accgccatgt atttctgtgc gagaggagg 300
acgtttttatt atgatagtag tgattatattt gactactggg gccagggaac cctggtcacc 360

A-2129-W0-PCT_Sequence_Listing_ST25.txt

gtgtcctca 369

<210> 263
<211> 369
<212> DNA
<213> Artificial Sequence

<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
V76 G05

<400> 263
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tcctgtaagg gttctggata cagttttggg agctactgga tcgcctgggt gcgccagatg 120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac 180
agcccggagt tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac 240
ctacagtgga gcagcctgaa ggcctcggac accgccatgt atttctgtgc gagacaaagg 300
acgttttatt atgatagtag tgattatagt gactactggg gccagggaac cctggtcacc 360
gtgtcctca 369

<210> 264
<211> 369
<212> DNA
<213> Artificial Sequence

<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
V84 H01

<400> 264
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cccgggaaag gcctggagtg gatggggatc atctatcctg gtgacagtga taccagatac 180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac 240
ctacagtgga gcagcctgaa ggcctcggac accgccatgt atttctgtgc gagacaaagg 300
acgttttatt atgatagtag tgattattcg gactactggg gccagggaac cctggtcacc 360
gtgtcctca 369

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 265
 <211> 22
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Secretory peptide #1

<400> 265

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1 5 10 15

Leu Arg Gly Ala Arg Cys
 20

<210> 266
 <211> 19
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Secretory peptide #2

<400> 266

Met Ala Trp Ala Leu Leu Leu Leu Thr Leu Leu Thr Gln Gly Thr Gly
 1 5 10 15

Ser Trp Ala

<210> 267

<400> 267
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<210> 268
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Secretory peptide #4

<400> 268

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15

Asp Thr Thr Gly
20

<210> 269
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Secretory peptide #5

<400> 269

Met Glu Trp Thr Trp Arg Val Leu Phe Leu Val Ala Ala Ala Thr Gly
1 5 10 15

Ala His Ser

<210> 270
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Secretory peptide #6

<400> 270

Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15

Asp Thr Thr Gly
20

<210> 271
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL3 Antibody ID V83

<400> 271

Gln Gln Ala Val Ser Phe Pro Arg Thr
1 5

<210> 272

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> Secretory peptide #8

<400> 272

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1 5 10 15

Val Leu Ser

<210> 273

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> Secretory peptide #9

<400> 273

Met Glu Trp Ser Trp Val Phe Leu Phe Phe Leu Ser Val Thr Thr Gly
1 5 10 15

Val His Ser

<210> 274

<211> 22

<212> PRT

<213> Artificial Sequence

<220>

<223> Secretory peptide #10

<400> 274

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Met Asp Ile Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Lys Cys
20

<210> 275
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Secretory peptide #11

<400> 275

Met Asp Ile Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Arg Cys
20

<210> 276
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Secretory peptide #12

<400> 276

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Thr Phe
20

<210> 277
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Secretory peptide #13

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<400> 277

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Arg Cys
20

<210> 278

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> Secretory peptide #14

<400> 278

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15

Val Gln Cys

<210> 279

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Secretory peptide #15

<400> 279

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1 5 10 15

Val Gln Cys Gln Glu
20

<210> 280

<211> 22

<212> PRT

<213> Artificial Sequence

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<220>

<223> Secretory peptide #16

<400> 280

Met Asp Met Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Arg Cys
20

<210> 281

<211> 217

<212> PRT

<213> Homo sapiens

<400> 281

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
115 120 125

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys
210 215

<210> 282
<211> 217
<212> PRT
<213> Homo sapiens

<400> 282

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu
50 55 60

Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys

A-2129-W0-PCT_Sequence_Listing_ST25.txt

85

90

95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
115 120 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys
210 215

<210> 283
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> MOG peptide 35-55

<400> 283

Met Glu Val Gly Trp Tyr Arg Ser Pro Phe Ser Arg Val Val His Leu
1 5 10 15

Tyr Arg Asn Gly Lys
20

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 284
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRL1 Consensus for 6E7 reduced Affinity variants

<220>
 <221> MISC_FEATURE
 <222> (1)..(1)
 <223> X is R OR A

<220>
 <221> MISC_FEATURE
 <222> (8)..(8)
 <223> X IS S OR R

<400> 284

Xaa	Ala	Ser	Gln	Gly	Ile	Ser	Xaa	Trp	Leu	Ala
1				5					10	

<210> 285
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRL2 Consensus for 6E7 reduced Affinity variants

<220>
 <221> MISC_FEATURE
 <222> (1)..(1)
 <223> X is A or S

<220>
 <221> MISC_FEATURE
 <222> (3)..(3)
 <223> X is S or G

<400> 285

Xaa	Ala	Xaa	Ser	Leu	Gln	Asn
1			5			

<210> 286

<211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRL3 Consensus for 6E7 reduced Affinity variants

<220>
 <221> MISC_FEATURE
 <222> (4)..(4)
 <223> X is D or V

<220>
 <221> MISC_FEATURE
 <222> (8)..(8)
 <223> X is R or L

<400> 286

Gln Gln Ala Xaa Ser Phe Pro Xaa Thr
 1 5

<210> 287
 <211> 5
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRH1 Consensus for 6E7 reduced Affinity variants

<220>
 <221> MISC_FEATURE
 <222> (2)..(2)
 <223> X is Y or E

<400> 287

Ser Xaa Trp Ile Ala
 1 5

<210> 288
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDRH2 Consensus for 6E7 reduced Affinity variants

<220>

<221> MISC_FEATURE

<222> (5)..(5)

<223> X is G or S

<400> 288

Ile	Ile	Tyr	Pro	Xaa	Asp	Ser	Asp	Thr	Arg	Tyr	Ser	Pro	Ser	Phe	Gln
1				5					10					15	

Gly

<210> 289

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH3 Consensus for 6E7 reduced Affinity variants

<220>

<221> MISC_FEATURE

<222> (3)..(3)

<223> X is T or G

<220>

<221> MISC_FEATURE

<222> (5)..(5)

<223> X is Y or R

<220>

<221> MISC_FEATURE

<222> (6)..(6)

<223> X is Y or G

<400> 289

Gln	Arg	Xaa	Phe	Xaa	Xaa	Asp	Ser	Ser	Asp	Tyr	Phe	Asp	Tyr
1				5					10				

<210> 290

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL1 Antibody ID V57 E10

<400> 290

Ala Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala
1 5 10

<210> 291

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL1 Antibody ID V90 H07

<400> 291

Arg Ala Ser Gln Gly Ile Ser Arg Trp Leu Ala
1 5 10

<210> 292

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL2 Antibody ID V10 A11

<400> 292

Ser Ala Ser Ser Leu Gln Asn
1 5

<210> 293

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL2 Antibody ID V70 F11

<400> 293

Ala Ala Gly Ser Leu Gln Asn
1 5

<210> 294

<211> 9

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL2 Antibody ID V23 B12

<400> 294

Gln Gln Ala Asp Ser Phe Pro Leu Thr

1 5

<210> 295

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> VL Amino Acid Sequence Antibody ID V10 A11

<400> 295

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp

20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile

35 40 45

Tyr Ser Ala Ser Ser Leu Gln Asn Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Ala Asp Ser Phe Pro Arg

85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys

100 105

<210> 296

<211> 107

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<212> PRT

<213> Artificial Sequence

<220>

<223> VL Amino Acid Sequence Antibody ID V23 B12

<400> 296

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Asn Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Ala Asp Ser Phe Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 297

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> VL Amino Acid Sequence Antibody ID V57 E10

<400> 297

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ala Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Asn Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Ala Asp Ser Phe Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 298
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> VL Amino Acid Sequence Antibody ID V70 F11

<400> 298

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Gly Ser Leu Gln Asn Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Ala Asp Ser Phe Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 299
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> VL Amino Acid Sequence Antibody ID V83 G12

<400> 299

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Asn Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Ala Val Ser Phe Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 300
<211> 107
<212> PRT
<213> Artificial Sequence

<220>

<223> VL Amino Acid Sequence Antibody ID V90 H07

<400> 300

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Arg Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Asn Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Ala Asp Ser Phe Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 301

<211> 4

<212> PRT

<213> Artificial Sequence

<220>

<223> FR1/

CDRH1 border

Antibody ID V30 C07

<400> 301

Ser Ser Phe Thr
1

<210> 302

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1 Antibody ID V90 H07

<400> 302

Ser Glu Trp Ile Ala
1 5

<210> 303

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH2 Antibody ID V44 D09

<400> 303

Ile Ile Tyr Pro Ser Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> 304

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH3 Antibody ID V9 A10

<400> 304

Gln Arg Gly Phe Tyr Tyr Asp Ser Ser Asp Tyr Phe Asp Tyr
1 5 10

<210> 305

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH3 Antibody ID V33 C10

<400> 305

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Gln Arg Thr Phe Tyr Gly Asp Ser Ser Asp Tyr Phe Asp Tyr
1 5 10

<210> 306
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRH3 Antibody ID V68 F09

<400> 306

Gln Arg Thr Phe Arg Tyr Asp Ser Ser Asp Tyr Phe Asp Tyr
1 5 10

<210> 307
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH Amino Acid Sequence Antibody ID V9 A10

<400> 307

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys
85 90 95

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Ala Arg Gln Arg Gly Phe Tyr Tyr Asp Ser Ser Asp Tyr Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 308
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH Amino Acid Sequence Antibody ID V30 C07

<400> 308

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Ser Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys
85 90 95

Ala Arg Gln Arg Thr Phe Tyr Tyr Asp Ser Ser Asp Tyr Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 309
<211> 123

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<212> PRT

<213> Artificial Sequence

<220>

<223> VH Amino Acid Sequence Antibody ID V33 C10

<400> 309

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys
85 90 95

Ala Arg Gln Arg Thr Phe Tyr Gly Asp Ser Ser Asp Tyr Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 310

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH Amino Acid Sequence Antibody ID V44 D09

<400> 310

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Ser Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys
85 90 95

Ala Arg Gln Arg Thr Phe Tyr Tyr Asp Ser Ser Asp Tyr Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 311
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH Amino Acid Sequence Antibody ID V68 F09

<400> 311

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys
85 90 95

Ala Arg Gln Arg Thr Phe Arg Tyr Asp Ser Ser Asp Tyr Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 312
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH Amino Acid Sequence Antibody ID V90 H07

<400> 312

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Glu
20 25 30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys
85 90 95

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Ala Arg Gln Arg Thr Phe Tyr Tyr Asp Ser Ser Asp Tyr Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 313
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
V10 A11

<400> 313
gacatccaga tgaccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgct gggcgagtca ggggtattagc agctgggtag cctgggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctattct gcatccagtt tgcaaaatgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttactt ttgtcaacag gctgacagtt tccctcgac ttttggccag 300
gggaccaagc tggagatcaa a 321

<210> 314
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
V23 B12

<400> 314
gacatccaga tgaccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgct gggcgagtca ggggtattagc agctgggtag cctgggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaaatgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttactt ttgtcaacag gctgacagtt tccctcttac ttttggccag 300

A-2129-W0-PCT_Sequence_Listing_ST25.txt

gggaccaagc tggagatcaa a 321

<210> 315
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
V57 E10

<400> 315
gacatccaga tgaccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtg cggcgagtca ggggtattagc agctgggtag cctgggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaaatgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttactt ttgtcaacag gctgacagtt tccctcgac ttttggccag 300
gggaccaagc tggagatcaa a 321

<210> 316
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
V70 F11

<400> 316
gacatccaga tgaccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca ggggtattagc agctgggtag cctgggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcagggagtt tgcaaaatgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttactt ttgtcaacag gctgacagtt tccctcgac ttttggccag 300
gggaccaagc tggagatcaa a 321

<210> 317
<211> 321

A-2129-W0-PCT_Sequence_Listing_ST25.txt

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<212> DNA
<213> Artificial Sequence

<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
      V83

<400> 317
gacatccaga tgaccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc      60
atcacttgtc gggcgagtc ggggtattagc agctgggtag cctgggtatca gcagaaacca      120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaaatgg ggtcccatca      180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct      240
gaagattttg caacttactt ttgtcaacag gctgtgagtt tccctcgac ttttggccag      300
gggaccaagc tggagatcaa a                                          321

<210> 318
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - LV Antibody ID
      V90 H07

<400> 318
gacatccaga tgaccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc      60
atcacttgtc gggcgagtc ggggtattagc agatgggtag cctgggtatca gcagaaacca      120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaaatgg ggtcccatca      180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct      240
gaagattttg caacttactt ttgtcaacag gctgacagtt tccctcgac ttttggccag      300
gggaccaagc tggagatcaa a                                          321

<210> 319
<211> 369
<212> DNA
<213> Artificial Sequence

<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
      V9 A10

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A-2129-W0-PCT_Sequence_Listing_ST25.txt

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<400> 319
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc      60
tcctgtaagg gttctggata cagttttacc agctactgga tcgcctgggt gcgccagatg      120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac      180
agcccgctcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac      240
ctacagtgga gcagcctgaa ggcctcggac accgccatgt atttctgtgc gagacaaagg      300
gggttttatt atgatagtag tgattatfff gactactggg gccagggaac cctggtcacc      360
gtgtcctca                                     369
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<210> 320
<211> 369
<212> DNA
<213> Artificial Sequence
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<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
      V10 A11
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V23 B12 V57 E10 V70 F11 V83 G12

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<400> 320
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc      60
tcctgtaagg gttctggata cagttttacc agctactgga tcgcctgggt gcgccagatg      120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac      180
agcccgctcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac      240
ctacagtgga gcagcctgaa ggcctcggac accgccatgt atttctgtgc gagacaaagg      300
acgttttatt atgatagtag tgattatfff gactactggg gccagggaac cctggtcacc      360
gtgtcctca                                     369
```

```
<210> 321
<211> 369
<212> DNA
<213> Artificial Sequence
```

```
<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
      V30 C07
```

A-2129-W0-PCT_Sequence_Listing_ST25.txt

```
<400> 321
gaggtgcagc tgggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc      60
tcctgtaagg gttctggatc gagttttacc agctactgga tcgcctgggt gcgccagatg      120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac      180
agcccgctcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac      240
ctacagtgga gcagcctgaa ggcctcggac accgccatgt atttctgtgc gagacaaagg      300
acgttttatt atgatagtag tgattatttt gactactggg gccaggggaac cctggtcacc      360
gtgtcctca                                     369
```

```
<210> 322
<211> 369
<212> DNA
<213> Artificial Sequence
```

```
<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
      V33 C10
```

```
<400> 322
gaggtgcagc tgggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc      60
tcctgtaagg gttctggata cagttttacc agctactgga tcgcctgggt gcgccagatg      120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac      180
agcccgctcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac      240
ctacagtgga gcagcctgaa ggcctcggac accgccatgt atttctgtgc gagacaaagg      300
acgttttatg gggatagtag tgattatttt gactactggg gccaggggaac cctggtcacc      360
gtgtcctca                                     369
```

```
<210> 323
<211> 369
<212> DNA
<213> Artificial Sequence
```

```
<220>
<223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
      V44 D09
```

```
<400> 323
```


A-2129-W0-PCT_Sequence_Listing_ST25.txt

gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc	60
tcctgtaagg gttctggata cagttttacc agctactgga tcgcctgggt gcgccagatg	120
cccgggaaag gcctggagtg gatggggatc atctatccta gtgactctga taccagatac	180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac	240
ctacagtgga gcagcctgaa ggcctcggac accgccatgt atttctgtgc gagacaaagg	300
acgttttatt atgatagtag tgattatfff gactactggg gccagggaac cctggtcacc	360
gtgtcctca	369

<210> 324
 <211> 369
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
 V68 F09

<400> 324	
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc	60
tcctgtaagg gttctggata cagttttacc agctactgga tcgcctgggt gcgccagatg	120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac	180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac	240
ctacagtgga gcagcctgaa ggcctcggac accgccatgt atttctgtgc gagacaaagg	300
acgttttaggt atgatagtag tgattatfff gactactggg gccagggaac cctggtcacc	360
gtgtcctca	369

<210> 325
 <211> 369
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Anti-TREM2 Antibody Variable Region Nucleic Acid - HV Antibody ID
 V90 H07

<400> 325	
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc	60

A-2129-W0-PCT_Sequence_Listing_ST25.txt

tcctgtaagg gttctggata cagttttacc agcgagtgga tcgcctgggt gcgccagatg	120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac	180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac	240
ctacagtgga gcagcctgaa ggcctcggac accgccatgt atttctgtgc gagacaaagg	300
acgttttatt atgatagtag tgattatfff gactactggg gccagggaac cctggtcacc	360
gtgtcctca	369

<210> 326
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> LC variable region sequence 24G6

<400> 326

Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Asp	Ser	Leu	Ala	Val	Ser	Leu	Gly
1				5				10					15		

Glu	Arg	Ala	Thr	Ile	Asn	Cys	Lys	Ser	Ser	Gln	Ser	Val	Leu	Tyr	Ser
			20					25					30		

Ser	Asn	Asn	Lys	His	Phe	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln
			35				40					45			

Pro	Pro	Lys	Leu	Leu	Ile	Tyr	Trp	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Val
		50				55					60				

Pro	Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr
65					70					75				80	

Ile	Ser	Ser	Leu	Gln	Ala	Glu	Asp	Val	Ala	Val	Tyr	Tyr	Cys	Gln	Gln
			85						90					95	

Tyr	Tyr	Ser	Thr	Pro	Leu	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile
			100					105					110		

Lys

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<210> 327
 <211> 119
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> HC variable region sequence 24G6

<400> 327

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Glu Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Lys Ala Tyr Thr Pro Met Ala Phe Phe Asp Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

<210> 328
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> LC variable region sequence 6E7

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<400> 328

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Ala Asp Ala Phe Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 329

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> HC variable region sequence 6E7

<400> 329

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Gly Ile Ile Tyr Pro Gly Asp Ala Asp Ala Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys
85 90 95

Ala Arg Gln Arg Thr Phe Tyr Tyr Asp Ser Ser Asp Tyr Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 330
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> LC variable region sequence 13E7

<400> 330

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30

Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Asp Asn Asn Phe Pro Pro

Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys
100 105

<210> 331
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> HC variable region sequence 13E7

<400> 331

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ala Asp Ala Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys
85 90 95

Ala Arg Arg Arg Gln Gly Ile Phe Gly Asp Ala Leu Asp Phe Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 332
<211> 107
<212> PRT

<213> Artificial Sequence

<220>

<223> LC variable region sequence 5E3

<400> 332

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Thr Tyr Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys
100 105

<210> 333

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> HC variable region sequence 5E3

<400> 333

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Pro Tyr Ser Gly Gly Thr Thr Ser Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Ser Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Ala Gly Tyr Leu Ala Leu Tyr Gly Thr Asp Val Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 334

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> AA sequence LC SST28347

<400> 334

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Asp Ile Val Met Thr Gln Ser Pro Asp Ser
20 25 30

Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser
35 40 45

Gln Ser Val Leu Tyr Ser Ser Asn Asn Lys His Phe Leu Ala Trp Tyr
50 55 60

Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<220>

<223> AA sequence HC SST28347

<400> 335

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Glu Val Gln Leu Leu Glu Ser Gly Gly Gly
20 25 30

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35 40 45

Phe Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly
50 55 60

Lys Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr
65 70 75 80

Tyr Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
85 90 95

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
100 105 110

Thr Ala Val Tyr Tyr Cys Ala Lys Ala Tyr Thr Pro Met Ala Phe Phe
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
130 135 140

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
145 150 155 160

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
165 170 175

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
180 185 190

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
195 200 205

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
210 215 220

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
225 230 235 240

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
245 250 255

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
260 265 270

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
275 280 285

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
290 295 300

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr
305 310 315 320

Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp
325 330 335

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
340 345 350

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
355 360 365

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
370 375 380

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
385 390 395 400

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
405 410 415

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
420 425 430

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
435 440 445

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
450 455 460

Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 336
<211> 468
<212> PRT
<213> Artificial Sequence

<220>
<223> AA sequence HC SST204812

<400> 336

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Glu Val Gln Leu Leu Glu Ser Gly Gly Gly
20 25 30

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35 40 45

Phe Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly
50 55 60

Lys Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr
65 70 75 80

Tyr Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn

A-2129-W0-PCT_Sequence_Listing_ST25.txt

85

90

95

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
 100 105 110

Thr Ala Val Tyr Tyr Cys Ala Lys Ala Tyr Thr Pro Met Ala Phe Phe
 115 120 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
 130 135 140

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Arg Ser Thr Ser
 145 150 155 160

Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
 165 170 175

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
 180 185 190

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
 195 200 205

Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys
 210 215 220

Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu
 225 230 235 240

Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
 245 250 255

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
 260 265 270

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
 275 280 285

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

A-2129-W0-PCT_Sequence_Listing_ST25.txt

290

295

300

Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr
305 310 315 320

Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
325 330 335

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
340 345 350

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
355 360 365

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
370 375 380

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
385 390 395 400

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
405 410 415

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
420 425 430

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
435 440 445

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
450 455 460

Ser Pro Gly Lys
465

<210> 337
<211> 236
<212> PRT
<213> Artificial Sequence

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<220>

<223> AA sequence SST29857

<400> 337

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Val Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Gly Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln
100 105 110

Ala Asp Ala Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 338
<211> 236
<212> PRT
<213> Artificial Sequence

<220>
<223> AA sequence LC SST29857

<400> 338

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Glu Ile Val Met Thr Gln Ser Pro Ala Thr
20 25 30

Leu Ser Val Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser
35 40 45

Gln Ser Val Ser Ser Asn Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln
50 55 60

Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile
65 70 75 80

Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln
100 105 110

Asp Asn Asn Phe Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Asp Ile

A-2129-W0-PCT_Sequence_Listing_ST25.txt

115

120

125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 339
<211> 236
<212> PRT
<213> Artificial Sequence

<220>
<223> AA sequence LC SST202443

<400> 339

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Glu Ile Val Met Thr Gln Ser Pro Ala Thr
20 25 30

Leu Ser Val Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser
35 40 45

A-2129-W0-PCT_Sequence_Listing_ST25.txt

Gln Ser Val Ser Ser Asn Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln
50 55 60

Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile
65 70 75 80

Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln
100 105 110

Asp Asn Asn Phe Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Asp Ile
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 340
<211> 473
<212> PRT

<213> Artificial Sequence

<220>

<223> AA sequence HC SST202443

<400> 340

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Glu Val Gln Leu Val Gln Ser Gly Ala Glu
20 25 30

Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly
35 40 45

Tyr Ser Phe Thr Ser Tyr Trp Ile Gly Trp Val Arg Gln Met Pro Gly
50 55 60

Lys Gly Leu Glu Trp Met Gly Ile Ile Tyr Pro Gly Asp Ala Asp Ala
65 70 75 80

Arg Tyr Ser Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys
85 90 95

Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp
100 105 110

Thr Ala Met Tyr Phe Cys Ala Arg Arg Arg Gln Gly Ile Phe Gly Asp
115 120 125

Ala Leu Asp Phe Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
130 135 140

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
145 150 155 160

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
165 170 175

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly

A-2129-W0-PCT_Sequence_Listing_ST25.txt

180

185

190

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
 195 200 205

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
 210 215 220

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
 225 230 235 240

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
 245 250 255

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 260 265 270

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 275 280 285

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
 290 295 300

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu
 305 310 315 320

Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His
 325 330 335

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
 340 345 350

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
 355 360 365

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
 370 375 380

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro

A-2129-W0-PCT_Sequence_Listing_ST25.txt

385 390 395 400

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
405 410 415

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
420 425 430

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
435 440 445

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
450 455 460

Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 341
<211> 236
<212> PRT
<213> Artificial Sequence

<220>
<223> AA sequence LC SST29825

<400> 341

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Gly Ile Ser Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Ser Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
65 70 75 80

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Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

Tyr Ser Thr Tyr Pro Phe Thr Phe Gly Gln Gly Thr Lys Val Asp Ile
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 342
<211> 470
<212> PRT
<213> Artificial Sequence

<220>
<223> AA sequence HC SST29825

<400> 342

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp

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1           5           10           15

Leu Arg Gly Ala Arg Cys Gln Val Gln Leu Val Gln Ser Gly Ala Glu
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Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly
      35                40                45

Tyr Thr Phe Thr Gly Tyr Tyr Ile His Trp Val Arg Gln Ala Pro Gly
      50                55                60

Gln Gly Leu Glu Trp Met Gly Trp Ile Asn Pro Tyr Ser Gly Gly Thr
      65                70                75                80

Thr Ser Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr
      85                90                95

Ser Thr Ser Ser Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp
      100                105                110

Thr Ala Val Tyr Tyr Cys Ala Arg Asp Ala Gly Tyr Leu Ala Leu Tyr
      115                120                125

Gly Thr Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
      130                135                140

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Arg Ser
      145                150                155                160

Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
      165                170                175

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
      180                185                190

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
      195                200                205

Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr

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210

215

220

Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr
 225 230 235 240

Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Glu
 245 250 255

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
 260 265 270

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
 275 280 285

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
 290 295 300

Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly
 305 310 315 320

Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp
 325 330 335

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
 340 345 350

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
 355 360 365

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
 370 375 380

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
 385 390 395 400

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
 405 410 415

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys

420

425

430

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
 435 440 445

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
 450 455 460

Ser Leu Ser Pro Gly Lys
 465 470

<210> 343
 <211> 339
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> LC variable region sequence SST28347 and SST204812

<400> 343
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 atcaactgca agtccagcca gagtgtttta tacagctcca acaataagca cttcttagct 120
 tgggtaccagc agaaaccagg acagcctcct aagctgctca tttactgggc atctaccgg 180
 gagtccggggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240
 atcagcagcc tgcaggctga agatgtggca gtttattact gtcagcaata ttatagtact 300
 ccgctcactt tcggcggagg gaccaaggtg gagatcaaa 339

<210> 344
 <211> 357
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> HC variable region sequence SST28347 and SST204812

<400> 344
 gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgagactc 60
 tcctgtgcag cctctggatt cacctttagc agctatgccca tgagctgggt ccgccaggct 120
 ccagggaagg gactggagtg ggtctcagct attagtggta gtggtggtag cacatactac 180

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gcagaatccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatac acagcctgag agccgaggac acggccgtat attactgtgc gaaggcgtat	300
acacctatgg cattctttga ctactggggc cagggaaccc tggtcaccgt ctcctca	357

<210> 345
 <211> 321
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> LC variable region sequence SST29857

<400> 345	
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gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca	180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct	240
gaagattttg caacttactt ttgtcaacag gctgacgctt tccctcgac ttttggccag	300
gggaccaagc tggagatcaa a	321

<210> 346
 <211> 369
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> HC variable region sequence SST29857

<400> 346	
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cccgggaaag gcctggagtg gatggggatc atctatcctg gtgacgctga tgccagatac	180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac	240
ctacagtgga gcagcctgaa ggcctcggac accgcatgt atttctgtgc gagacaaagg	300
acgttttatt atgatagtag tgattatatt gactactggg gccagggaac cctggtcacc	360
gtgtcctca	369

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<210> 347
 <211> 321
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> LC variable region sequence SST202443

<400> 347
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 ggccaggctc ccaggctcct catctatggt gcttccacca gggccactgg tattccagcc 180
 aggttcagtg gcagtgggtc tgggacagag ttactctca ccatcagcag cctgcagcct 240
 gaagattttg cagtttatta ctgtctgcag gataataatt tccctccac tttcggccaa 300
 gggaccaaag tggatatcaa a 321

<210> 348
 <211> 363
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> HC variable region sequence SST202443

<400> 348
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 cccgggaaag gcctggagtg gatggggatc atctatcctg gagatgctga tgccagatac 180
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 ctgcagtgga gcagcctgaa ggcctcggac accgccatgt atttctgtgc gaggcggaga 300
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 tca 363

<210> 349
 <211> 321
 <212> DNA
 <213> Artificial Sequence

A-2129-W0-PCT_Sequence_Listing_ST25.txt

<220>

<223> LC variable region sequence SST29825

<400> 349

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gggaaagccc ctaaatccct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca	180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct	240
gaagattttg caacttatta ctgccaacag tatagtactt acccattcac tttcggccaa	300
gggaccaaag tggatatcaa a	321

<210> 350

<211> 363

<212> DNA

<213> Artificial Sequence

<220>

<223> HC variable region sequence SST29825

<400> 350

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cctggacaag ggcttgagtg gatgggatgg atcaaccctt acagtgggtg cacaacctct	180
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atggaactga gcaggctgag atctgacgac acggccgtgt attactgtgc gagagatgca	300
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<210> 351

<211> 726

<212> DNA

<213> Artificial Sequence

<220>

<223> NA sequence LC SST28347

<400> 351

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ttagcttgggt accagcagaa accaggacag cctcctaagc tgctcattta ctgggcatct	240
acccgggagt ccgggggtccc tgaccgattc agtggcagcg ggtctgggac agatttcact	300
ctcaccatca gcagcctgca ggctgaagat gtggcagttt attactgtca gcaatattat	360
agtactccgc tcactttcgg cggagggacc aaggtggaga tcaaacgaac ggtggctgca	420
ccatctgtct tcatcttccc gccatctgat gagcagttga aatctggaac tgcctctgtt	480
gtgtgcctgc tgaataactt ctatcccaga gaggccaaag tacagtggaa ggtggataac	540
gccctccaat cgggtaactc ccaggagagt gtcacagagc aggacagcaa ggacagcacc	600
tacagcctca gcagcaccct gacgctgagc aaagcagact acgagaaaca caaagtctac	660
gcctgcgaag tcacccatca gggcctgagc tcgcccgtca caaagagctt caacagggga	720
gagtgt	726

<210> 352
 <211> 1413
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> NA sequence HC SST28347

<400> 352	
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ctgtatctgc aaatgaacag cctgagagcc gaggacacgg ccgtatatta ctgtgcgaag	360
gcgtatacac ctatggcatt ctttgactac tggggccagg gaaccttggt caccgtctcc	420
tcagcctcca ccaagggccc atcgggtcttc cccctggcac cctcctcaa gagcacctct	480
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cccaaattctt gtgacaaaac tcacacatgc ccaccgtgcc cagcacctga actcctgggg	780
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tggtacgtgg acggcgtgga ggtgcataat gccaaagaca agccgtgcga ggagcagtac	960
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tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgcccc atcccgggag	1140
gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tcccagcgac	1200
atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cagcctccc	1260
gtgctggact ccgacggctc cttcttcctc tatagcaagc tcaccgtgga caagagcagg	1320
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acgcagaaga gcctctccct gtctccgggc aaa	1413

<210> 353
 <211> 1404
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> NA sequence HC SST204812

<400> 353	
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cgctgtgagg tgcagctggt ggagtctggg ggaggcttgg tacagcctgg ggggtccctg	120
agactctcct gtgcagcctc tggattcacc tttagcagct atgcatgag ctgggtccgc	180
caggctccag ggaagggact ggagtgggtg tcagctatta gtggtagtgg tggtagcaca	240
tactacgcag aatccgtgaa gggccggttc accatctcca gagacaattc caagaacacg	300
ctgtatctgc aaatgaacag cctgagagcc gaggacacgg ccgtatatta ctgtgcgaag	360

A-2129-W0-PCT_Sequence_Listing_ST25.txt

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gagagcacag cggccctggg ctgcctgggc aaggactact tccccgaacc ggtgacggtg	540
tcgtggaact caggcgtctt gaccagcggc gtgcacacct tcccagctgt cctacagtcc	600
tcaggactct actccctcag cagcgtgggt accgtgccct ccagcaactt cggcaccag	660
acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag	720
cgaaatgtt gtgtcgagt cccaccgtgc ccagcacctg aactcctggg gggaccgtca	780
gtcttcctct tcccccaaa acccaaggac accctcatga tctcccggac ccctgaggtc	840
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gacggcgtgg aggtgcataa tgccaagaca aagccgtgcg aggagcagta cggcagcacg	960
taccgttgcg tcagcgtcct caccgtcctg caccaggact ggctgaatgg caaggagtac	1020
aagtgcaagg tgtccaacaa agccctccca gccccatcg agaaaaccat ctccaaagcc	1080
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aagaaccagg tcagcctgac ctgcctgggc aaaggcttct atcccagcga catcgccgtg	1200
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<210> 354
 <211> 708
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> NA sequence LC SST29857

<400> 354	
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cgctgtgaca tccagatgac ccagtctcca tcttccgtgt ctgcatctgt aggagacaga	120
gtcaccatca cttgtcgggc gagtcagggt attagcagct ggtagcctg gtatcagcag	180

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cagcctgaag attttgcaac ttacttttgt caacaggctg acgctttccc tcgcactttt	360
ggccagggga ccaagctgga gatcaaacga acggtggctg caccatctgt cttcatcttc	420
ccgccatctg atgagcagtt gaaatctgga actgcctctg ttgtgtgcct gctgaataac	480
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ctgacgctga gcaaagcaga ctacgagaaa cacaaagtct acgcctgcga agtcacccat	660
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<210> 355
 <211> 1416
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> NA sequence HC SST29857

<400> 355	
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caaaggacgt tttattatga tagtagtgat tattttgact actggggcca gggaaccctg	420
gtcaccgtgt cctcagcctc caccaagggc ccatcggtct tccccctggc gccagctcc	480
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gtcctacagt cctcaggact ctactccctc agcagcgtgg tgaccgtgcc ctccagcaac	660
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accctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc	900
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgtg cgaggagcag	960
tacggcagca cgtaccgttg cgtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat	1020
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gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct	1260
cccgtgctgg actccgacgg ctcttcttc ctctatagca agctcaccgt ggacaagagc	1320
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<210> 356
 <211> 708
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> NA sequence LC SST202443

<400> 356	
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gccaccctct cctgcagggc cagtcagagt gttagcagca acttagcctg gttccagcag	180
aaacctggcc aggctcccag gtcctcatc tatggtgctt ccaccagggc cactgggtatt	240
ccagccaggt tcagtggcag tgggtctggg acagagttca ctctcaccat cagcagcctg	300
cagcctgaag attttgagcgt ttattactgt ctgcaggata ataatttccc tcccactttc	360
ggccaaggga ccaaagtga tatcaaacga acgggtggctg caccatctgt cttcatcttc	420
ccgccatctg atgagcagtt gaaatctgga actgcctctg ttgtgtgcct gctgaataac	480
ttctatccca gagaggccaa agtacagtgg aaggtggata acgccctcca atcgggtaac	540

A-2129-W0-PCT_Sequence_Listing_ST25.txt

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cagggcctga gctcgcccggt cacaaagagc ttcaacaggg gagagtgt	708

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 <211> 1419
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> NA sequence HC SST202443

<400> 357	
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A-2129-W0-PCT_Sequence_Listing_ST25.txt

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10

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<223> Peptides from epitope mapping experiments

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Gly Asp Leu Trp Phe Pro

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