[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

[0006] The present disclosure 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

disclosure 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 examples, the present disclosure provides isolated agonist antigen binding proteins that specifically bind to human TREM2 and induce or activate one or more TREM2-mediated functions.

[0006a] In one aspect, the present disclosure refers to an isolated agonist antigen binding protein that specifically binds to human TREM2, wherein the agonist antigen binding protein increases: a) TREM2-mediated 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, b) TREM2-mediated 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, or c) TREM2-mediated pSyk levels 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.

[0006b] In another aspect, the present disclosure refers to an isolated agonist antigen binding protein that specifically binds to human TREM2, wherein the agonist antigen binding protein increases TREM2-mediated 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, and wherein the agonist antigen binding protein competes with a reference antibody for binding to human TREM2, wherein the reference antibody comprises: (a) 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: 10, CDRL2 comprises the sequence of SEQ ID NO: 23 and CDRL3 comprises the sequence of SEQ ID NO: 37, and wherein CDRH1 comprises the sequence of SEQ ID NO: 81, CDRL2 comprises the sequence of SEQ ID NO: 91, and CDRL3 comprises the sequence of SEQ ID NO: 101; (b) a light chain variable region comprising the sequence of SEQ ID NO: 330 and a heavy chain variable region comprising the sequence of SEQ ID NO: 331; (c) 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; (d) 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; (e) 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; (f) 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; or (g) 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.

[0006c] In another aspect, the present disclosure refers to an isolated agonist antigen binding protein that specifically binds to human TREM2, wherein the agonist antigen binding protein comprises 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 a sequence selected from SEQ ID NOs: 5-18 or a variant thereof having one, two, three or four amino acid substitutions; CDRL2 comprises a sequence selected from SEQ ID NOs: 19-30 or a variant thereof having one, two, three or four amino acid substitutions; CDRL3 comprises a sequence selected from SEQ ID NOs: 31-45 or a variant thereof having one, two, three or four amino acid substitutions; CDRH1 comprises a sequence selected from SEQ ID NOs: 77-86 or a variant thereof having one, two, three or four amino acid substitutions; CDRH2 comprises a sequence selected from SEQ ID NOs: 87-94 or a variant thereof having one, two, three or four amino acid substitutions; and CDRH3 comprises a sequence selected from SEQ ID NOs: 95-109 or a variant thereof having one, two, three or four amino acid substitutions.

[0006d] In another aspect, the present disclosure refers to an isolated polynucleotide that encodes the agonist antigen binding protein as described herein.

[0006e] In yet another aspect, the present disclosure refers to an expression vector comprising the polynucleotide as described herein.

[0006f] In yet another aspect, the present disclosure refers to a host cell comprising the expression vector as described herein.

[0006g] In yet another aspect, the present disclosure refers to a method of producing an agonist antigen binding protein that specifically binds to human TREM2 comprising culturing the host cell as described herein under conditions that allow expression of the antigen binding protein; and recovering the antigen binding protein from the culture medium or host cell.

[0006h] In yet another aspect, the present disclosure refers to the use of the agonist antigen binding protein as described herein in the manufacture of a medicament for treating or preventing a condition associated with a loss of function of human TREM2 in a patient in need thereof, wherein the condition is Alzheimer's disease, Nasu-Hakola disease, frontotemporal dementia, multiple sclerosis, prion disease, or stroke.

[0007] In some examples, 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 examples, 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 examples, 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 examples, 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 examples, the TREM2 agonist antigen binding proteins do not cross-react with other TREM proteins, such as human TREM1. Thus, in one example, 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 disclosure 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 example, 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 example, 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 example, 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 example, 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 examples, the TREM2 agonist antigen binding proteins of the disclosure 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 examples, 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 examples, 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 example, 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 example, 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 example, 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 example, 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 example, 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 example, 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 examples, 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 examples, 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 example, 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 examples, 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 example, 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 examples, the mutation is V64G, V64A, Q79E, S80P, S80A, W94Y, W94S, P100R, P100Q, or combinations thereof. In another example, 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 examples can be selected from L60S, L60P, L60D, L60A, D92E, D92Q, D92T, D92N, S93A, S93N, S93Q, S93V, or combinations thereof. In yet another example, 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 examples, the mutation can be N56S, N56T, N56Q, N56E, G57A, G57V, D92E, D92Q, D92T, D92N, S93A, S93N, S93Q, S93V, or combinations thereof. In certain examples, the mutation is N56S, N56Q, G57A, D92E, D92Q, S93A, or combinations thereof. In still another example, 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 examples, the mutation is F36Y, K61R, P100Q, or combinations thereof. In another example, 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 example, the mutation is F91V.

[0013] In certain examples, 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 examples, 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 example, 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 examples, 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 example, 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 examples, the mutation is M19K, D55E, S56A, D57E, T58A, W104Y, W104T, or combinations thereof. In another example, 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 examples, 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 example, 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 examples 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 examples, the mutation is D55E, D55Q, S56A, D57E, T58A, D105E, D105N, S106A, or combinations thereof. In still another example, 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 examples, the mutation is L43Q, R85S, D99E, G100A, G100Y, T116L, or combinations thereof. In another example, 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 examples, the mutation can be selected from D62E, D62Q, D62T, D62N, S63A, S63Q, S63V, or combinations thereof. In some examples, the mutation is D62E, D62Q, S63A, or combinations thereof.

[0014] In some examples, 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 examples, the TREM2 agonist antigen binding proteins comprise one or more CDRs of anti-TREM2 antibody variants with improved binding affinity. In these and other examples, 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 example, 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 examples, 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 examples, the CDRH2 consensus sequence is $X_1IYPGDSDX_2RX_3X_4PX_5FQX_6$ (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. The CDRH3 consensus may be $X_1RTFYYDSSDYX_2DY$ (SEQ ID NO: 142), where X_1 is Q, G, S, or M; and X_2 is F or S. In further examples, the CDRL2 of the TREM2 agonist antigen binding proteins of the disclosure may comprise a sequence selected from SEQ ID NOs: 26 and 143-147. In still further examples, the CDRL3 of the TREM2 agonist antigen binding proteins of

the disclosure may comprise a sequence selected from SEQ ID NOs: 43 and 148-152. In some examples, the CDRH2 of the TREM2 agonist antigen binding proteins of the disclosure may comprise a sequence selected from SEQ ID NOs: 91 and 170-175. In other examples, the CDRH3 of the TREM2 agonist antigen binding proteins of the disclosure may comprise a sequence selected from SEQ ID NOs: 176-179.

[0015] In other examples, the TREM2 agonist antigen binding proteins comprise one or more CDRs of anti-TREM2 antibody variants with reduced binding affinity. In these and other examples, 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 example, 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 examples, 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 examples, 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 examples, the CDRH1 consensus sequence is SX_1WIA (SEQ ID NO: 287), where X_1 is Y or E. In related examples, the CDRH2 consensus sequence is IIYPX_1DSDTRYSPSFQG (SEQ ID NO: 288), where X_1 is G or S. The CDRH3 consensus may be QRX_1F$X_2$$X_3$DSSDYFDY (SEQ ID NO: 289), where X_1 is T or G; X_2 is Y or R; and X_3 is Y or G. In some examples, the CDRL1 of the TREM2 agonist antigen binding proteins of the disclosure may comprise a sequence selected from SEQ ID NOs: 16, 290, and 291. In further examples, the CDRL2 of the TREM2 agonist antigen binding proteins of the disclosure may comprise a sequence selected from SEQ ID NOs: 28, 292, and 293. In still further examples, the CDRL3 of the TREM2 agonist antigen binding proteins of the disclosure may comprise a sequence selected from SEQ ID NOs: 43, 294, and 271. In some examples, the CDRH1 of the TREM2 agonist antigen binding proteins of the disclosure may comprise the sequence of SEQ ID NO: 85 or SEQ ID NO: 302. In other examples, the CDRH2 of the TREM2 agonist antigen binding proteins of the disclosure may comprise the sequence of SEQ ID NO: 91 or SEQ ID NO: 303. In still other examples, the CDRH3 of the TREM2 agonist antigen binding proteins of the disclosure may comprise a sequence selected from SEQ ID NOs: 107 and 304-306.

[0016] In certain examples, 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 examples, 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 examples, 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 examples described herein, including the examples 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 examples, the monoclonal antibody or binding fragment thereof is a chimeric antibody or binding fragment thereof. In other examples, the monoclonal antibody or binding fragment thereof is a humanized antibody or binding fragment thereof. In yet other examples, 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 example, the monoclonal antibody is a human IgG1 antibody. In another particular example, the monoclonal antibody is a human IgG2 antibody.

[0018] In certain examples 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 examples, the antibody comprises one or more mutations to reduce or eliminate glycosylation. In such examples, 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 example, the aglycosylated antibody comprises R292C and V302C mutations (according to the EU numbering scheme) in its heavy chain. In certain examples, 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 examples 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 example, the anti-TREM2 agonist antibody comprises a C131S mutation (according to the EU numbering scheme) in its heavy chain. In another example, 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 example, 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 examples, the TREM2 agonist antigen binding proteins of the disclosure 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 example, 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 examples, the TREM2 agonist antigen binding proteins of the disclosure 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 examples, the TREM2 agonist antigen binding proteins of the disclosure 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 disclosure 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 examples, the present disclosure includes methods for producing the TREM2 agonist antigen binding proteins, including anti-TREM2 agonist monoclonal antibodies and binding fragments thereof. In one example, 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. In another aspect, the present disclosure also provides a pharmaceutical composition comprising a TREM2 agonist antigen binding protein described herein and a pharmaceutically acceptable excipient.

[0024] In certain examples, the present disclosure 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 example, the method comprises administering to the patient an effective amount of any of the TREM2 agonist antigen binding proteins described herein. In some examples, the condition to be treated, prevented, or ameliorated is Alzheimer's disease. In other examples, 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 disclosure. For instance, in some examples, the patient has a genotype associated with an increased risk of developing Alzheimer's disease, such as the genotypes described herein. In further examples, 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 disclosure 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 example, the method comprises administering to the patient an effective amount of any of the TREM2 agonist antigen binding proteins described herein. In some

examples, 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 examples, 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

CLAIMS

What is claimed:

1. An isolated agonist antigen binding protein that specifically binds to human TREM2, wherein the agonist antigen binding protein increases:
a) TREM2-mediated 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,
b) TREM2-mediated 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, or
c) TREM2-mediated pSyk levels 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.

2. The isolated agonist antigen binding protein of claim 1, wherein the agonist antigen binding protein specifically binds to human TREM2 with a K_D less than 50 nM or less than 10 nM.

3. The isolated agonist antigen binding protein of claim 1, wherein the agonist antigen binding protein does not specifically bind to human TREM1.

4. An isolated agonist antigen binding protein that specifically binds to human TREM2, wherein the agonist antigen binding protein increases TREM2-mediated 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, and wherein the agonist antigen binding protein competes with a reference antibody for binding to human TREM2, wherein the reference antibody comprises:

(a) 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: 10, CDRL2 comprises the sequence of SEQ ID NO: 23 and CDRL3 comprises the sequence of SEQ ID NO: 37, and wherein CDRH1 comprises the sequence of SEQ ID NO: 81, CDRL2 comprises the sequence of SEQ ID NO: 91, and CDRL3 comprises the sequence of SEQ ID NO: 101;

(b) a light chain variable region comprising the sequence of SEQ ID NO: 330 and a heavy chain variable region comprising the sequence of SEQ ID NO: 331;

(c) 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;

(d) 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;

(e) 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;

(f) 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; or

(g) 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.

5. An isolated agonist antigen binding protein that specifically binds to human TREM2, wherein the agonist antigen binding protein comprises 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 a sequence selected from SEQ ID NOs: 5-18 or a variant thereof having one, two, three or four amino acid substitutions; CDRL2 comprises a sequence selected from SEQ ID NOs: 19-30 or a variant thereof having one, two, three or four amino acid substitutions; CDRL3 comprises a sequence selected from SEQ ID NOs: 31-45 or a variant thereof having one, two, three or four amino acid substitutions; CDRH1 comprises a sequence selected from SEQ ID NOs: 77-86 or a variant thereof having one, two, three or four amino acid substitutions; CDRH2 comprises a sequence selected from SEQ ID NOs: 87-94 or a variant thereof having one, two, three or four amino acid substitutions; and CDRH3 comprises a sequence selected from SEQ ID NOs: 95-109 or a variant thereof having one, two, three or four amino acid substitutions.

6. The isolated agonist antigen binding protein of claim 5, wherein CDRL1 comprises a sequence selected from SEQ ID NOs: 5-18; CDRL2 comprises a sequence selected from SEQ ID NOs: 19-30; CDRL3 comprises a sequence selected from SEQ ID NOs: 31-45; CDRH1

comprises a sequence selected from SEQ ID NOs: 77-86; CDRH2 comprises a sequence selected from SEQ ID NOs: 87-94; and CDRH3 comprises a sequence selected from SEQ ID NOs: 95-109.

7. The isolated agonist antigen binding protein of claim 5, wherein the light chain variable region comprises (i) a sequence that is at least 90% identical to a sequence selected from SEQ ID NOs: 46-63, (ii) a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 46-63, or (iii) a sequence selected from SEQ ID NOs: 46-63.

8. The isolated agonist antigen binding protein of claim 7, wherein the light chain variable region comprises

a) the sequence of SEQ ID NO: 54, or

b) 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, or

c) 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, wherein 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, or P100G, or combinations thereof.

9. The isolated agonist antigen binding protein of claim 7, wherein the light chain variable region comprises

a) the sequence of SEQ ID NO: 55 or

b) the sequence of SEQ ID NO: 55 with a mutation at one or more amino acid positions 64, 79, 80, 94, and/or 100, or

c) the sequence of SEQ ID NO: 55 with a mutation at one or more amino acid positions 64, 79, 80, 94, and/or 100, wherein the mutation is V64G, V64A, Q79E, Q79D, S80P, S80A, W94F, W94Y, W94S, W94T, W94A, W94H, W94I, W94Q, P100R, P100Q, or P100G, or combinations thereof.

10. The isolated agonist antigen binding protein of claim 7, wherein the light chain variable region comprises

a) the sequence of SEQ ID NO: 60 or
b) the sequence of SEQ ID NO: 60 with a mutation at one or more amino acid positions 60, 92, and/or 93, or
c) the sequence of SEQ ID NO: 60 with a mutation at one or more amino acid positions 60, 92, and/or 93, wherein the mutation is L60S, L60P, L60D, L60A, D92E, D92Q, D92T, D92N, S93A, S93N, S93Q, or S93V, or combinations thereof.

11. The isolated agonist antigen binding protein of claim 7, wherein the light chain variable region comprises
a) the sequence of SEQ ID NO: 61 or
b) the sequence of SEQ ID NO: 61 with a mutation at one or more amino acid positions 56, 57, 92, and/or 93, or
c) the sequence of SEQ ID NO: 61 with a mutation at one or more amino acid positions 56, 57, 92, and/or 93, wherein the mutation is N56S, N56T, N56Q, N56E, G57A, G57V, D92E, D92Q, D92T, D92N, S93A, S93N, S93Q, or S93V, or combinations thereof.

12. The isolated agonist antigen binding protein of claim 7, wherein the light chain variable region comprises
a) the sequence of SEQ ID NO: 62 or
b) the sequence of SEQ ID NO: 62 with a mutation at amino acid position 36, 46, 61 and/or 100, or
c) the sequence of SEQ ID NO: 62 with a mutation at amino acid position 36, 46, 61 and/or 100, wherein the mutation is F36Y, S46L, S46R, S46V, S46F, K61R, P100Q, P100G, or P100R or combinations thereof.

13. The isolated agonist antigen binding protein of claim 7, wherein the light chain variable region comprises
a) the sequence of SEQ ID NO: 52 or
b) the sequence of SEQ ID NO: 52 with a mutation at amino acid position 91, or
c) the sequence of SEQ ID NO: 52 with a mutation at amino acid position 91, wherein the mutation is F91V, F91I, F91T, F91L, or F91D or combinations thereof.

14. The isolated agonist antigen binding protein of any one of claim 5 to 13, wherein the heavy chain variable region comprises (i) a sequence that is at least 90% identical to a sequence selected from SEQ ID NOs: 110-126, (ii) a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 110-126, or (iii) a sequence selected from SEQ ID NOs: 110-126.

15. The isolated agonist antigen binding protein of claim 14, wherein the heavy chain variable region comprises

a) the sequence of SEQ ID NO: 117 or

b) 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, or

c) 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, wherein 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, or W104Q, or combinations thereof.

16. The isolated agonist antigen binding protein of claim 14, wherein the heavy chain variable region comprises

a) the sequence of SEQ ID NO: 118 or

b) 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, or

c) 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, wherein 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, or W104Q, or combinations thereof.

17. The isolated agonist antigen binding protein of claim 14, wherein the heavy chain variable region comprises

a) the sequence of SEQ ID NO: 123 or

b) 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, or

c) 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, wherein the mutation is H27Y, H27D, H27F, H27N, D55E, D55Q, D55N, D55T, S56A, S56Q, S56V, D57S, D57E, D57Q, T58A, T58V, D105E, D105Q, D105T, D105N, D105G, S106A, S106Q, S106V, or S106T, or combinations thereof.

18. The isolated agonist antigen binding protein of claim 14, wherein the heavy chain variable region comprises

a) the sequence of SEQ ID NO: 124 or

b) 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, or

c) 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, wherein the mutation is D55E, D55Q, D55N, D55T, S56A, S56Q, S56V, D57S, D57E, D57Q, T58A, T58V, D105E, D105Q, D105T, D105N, D105G, S106A, S106Q, S106V, or S106T, or combinations thereof.

19. The isolated agonist antigen binding protein of claim 14, wherein the heavy chain variable region comprises

a) the sequence of SEQ ID NO: 125 or

b) 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, or

c) 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, wherein the mutation is L43Q, L43K, L43H, I76T, R85S, R85G, R85N, R85D, D99E, D99Q, D99S, D99T, G100A, G100Y, G100V, T116L, T116M, T116P, or T116R, or combinations thereof.

20. The isolated agonist antigen binding protein of claim 14, wherein the heavy chain variable region comprises

a) the sequence of SEQ ID NO: 115 or

b) the sequence of SEQ ID NO: 115 with a mutation at amino acid position 62 and/or 63, or

c) the sequence of SEQ ID NO: 115 with a mutation at amino acid position 62 and/or 63, wherein the mutation is D62E, D62Q, D62T, D62N, S63A, S63Q, or S63V, or combinations thereof.

21. The isolated agonist antigen binding protein of any one of claims 1 to 20, wherein the agonist antigen binding protein is a monoclonal antibody or binding fragment thereof.

22. The isolated agonist antigen binding protein of claim 21, wherein the monoclonal antibody or binding fragment thereof is a chimeric antibody or binding fragment thereof, a humanized antibody or binding fragment thereof, or a fully human antibody or binding fragment thereof.

23. The isolated agonist antigen binding protein of claim 21, wherein the monoclonal antibody is a human IgG1, IgG2, IgG3, or IgG4 antibody.

24. The isolated agonist antigen binding protein of claim 23, wherein the monoclonal antibody is a human IgG2 antibody.

25. The isolated agonist antigen binding protein of claim 24, wherein the monoclonal antibody comprises a C131S mutation according to EU numbering in its heavy chain or wherein the monoclonal antibody comprises a C214S mutation according to EU numbering in its light chain and a C220S mutation according to EU numbering in its heavy chain.

26. The isolated agonist antigen binding protein of claim 23, wherein the monoclonal antibody is a human IgG1 antibody.

27. The isolated agonist antigen binding protein of claim 26, wherein the monoclonal antibody is an aglycosylated human IgG1 antibody.

28. The isolated agonist antigen binding protein of claim 27, wherein the monoclonal antibody comprises a mutation at amino acid position N297 according to EU numbering in its heavy chain.

29. The isolated agonist antigen binding protein of claim 28, wherein the mutation is N297G.

30. The isolated agonist antigen binding protein of claim 28 or 29, wherein the monoclonal antibody further comprises R292C and V302C mutations according to EU numbering in its heavy chain.

31. The isolated agonist antigen binding protein of claim 21, wherein the monoclonal antibody comprises an Fc region from a human IgG1 antibody and a CH1 region and hinge region from a human IgG2 antibody.

32. The isolated agonist antigen binding protein of claim 31, wherein the monoclonal antibody comprises a mutation at amino acid position N297 according to EU numbering in its heavy chain.

33. The isolated agonist antigen binding protein of claim 32, wherein the mutation is N297G.

34. The isolated agonist antigen binding protein of claim 32 or 33, wherein the monoclonal antibody further comprises R292C and V302C mutations according to EU numbering in its heavy chain.

35. The isolated agonist antigen binding protein of claim 31, wherein the monoclonal antibody comprises a C131S mutation according to EU numbering in its heavy chain.

36. The isolated agonist antigen binding protein of claim 31, wherein the monoclonal antibody comprises a C214S mutation according to EU numbering in its light chain and a C220S mutation according to EU numbering in its heavy chain.

37. A pharmaceutical composition comprising the agonist antigen binding protein of any one of claims 1 to 36 and a pharmaceutically acceptable excipient.

38. An isolated polynucleotide that encodes the agonist antigen binding protein of any one of claims 1 to 36.

39. An expression vector comprising the polynucleotide of claim 38.

40. A host cell comprising the expression vector of claim 39.

41. A method of producing an agonist antigen binding protein that specifically binds to human TREM2 comprising culturing the host cell of claim 40 under conditions that allow expression of the antigen binding protein; and recovering the antigen binding protein from the culture medium or host cell.

42. Use of the agonist antigen binding protein of any one of claims 1 to 36 in the manufacture of a medicament for treating or preventing a condition associated with a loss of function of human TREM2 in a patient in need thereof, wherein the condition is Alzheimer's disease, Nasu-Hakola disease, frontotemporal dementia, multiple sclerosis, prion disease, or stroke.

43. The agonist antigen binding protein of any one of claims 1 to 36 for use in therapy.