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 another aspect, the present disclosure refers to 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; CDRH1 comprises the amino acid sequence of: SYWIG (SEQ ID NO:81); CDRH2 comprises the amino acid sequence of: IIYPGDADARYSPSFQG; and CDRH3 comprises the amino acid sequence of: RRQGIFGDALDF.

[0006b] In another aspect, the present disclosure refers to an anti-human TREM2 (hTREM2) antibody, comprising a light chain having the amino acid sequence of: EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWFQQKPGQAPRLLIYGASTRATGIPARFSG SGSGTEFTLTISSLQPEDFAVYYCLQDNNFPPTFGQGTKVDIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC; and a heavy chain having the amino acid sequence of: EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIYPGDADARYS PSFQGQVTISADKSISTAYLQWSSLKASDTAMYFCARRRQGIFGDALDFWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV

KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK.

[0006c] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the anti-hTREM2 antibody as disclosed herein and a pharmaceutically acceptable excipient.

[0006d] In another aspect, the present disclosure refers to an isolated polynucleotide that encodes the anti-hTREM2 antibody 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 anti-hTREM2 antibody that specifically binds to human TREM2 comprising culturing the host cell as described herein 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.

[0006h] In one example, 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.

CLAIMS

What is claimed:

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;
CDRH1 comprises the amino acid sequence of: SYWIG (SEQ ID NO: 81);
CDRH2 comprises the amino acid sequence of: IIYPGDADARYSPSFQG; and
CDRH3 comprises the amino acid sequence of: RRQGIFGDALDF.

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, 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 claim 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 claim 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 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 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
SGTEFTLTISSLQPEDFAVYYCLQDNNFPPTFGQGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV
THQGLSSPVTKSFNRGEC; and

a heavy chain having the amino acid sequence of:
EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIYPGDADARYSPSF
QGQVTISADKSISTAYLQWSSLKASDTAMYFCARRRQGIFGDALDFWGQGTLVTVSSASTKGPS
VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP
SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR
TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
K.

13. A pharmaceutical composition comprising the anti-hTREM2 antibody of claim 1 and a pharmaceutically acceptable excipient.

14. A polynucleotide that encodes the anti-hTREM2 antibody of claim 1.

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.