

ANTI-TREM2 ANTIBODIES AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/541,019, filed August 3, 2017 and 62/636,095 filed February 27, 2018, which are hereby incorporated by reference in their entirety.

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: 735022001840SEQLIST.TXT, date recorded: August 2, 2018, size: 238 KB).

FIELD OF THE PRESENT DISCLOSURE

[0003] The present disclosure relates to anti-TREM2 antibodies and therapeutic uses of such antibodies.

BACKGROUND OF THE PRESENT DISCLOSURE

[0004] Triggering receptor expressed on myeloid cells-2 (TREM2) is an immunoglobulin-like receptor that is expressed, for example, on myeloid lineage cells.

[0005] TREM2 activity has been implicated in diseases, disorders, and conditions, such as frontotemporal dementia (FTD), Alzheimer's disease, Parkinson's disease, stroke/ischemic brain injury, multiple sclerosis, and Nasu-Hakola disease (Neumann, H et al., (2007) J Neuroimmunol 184: 92-99; Takahashi, K et al., (2005) J Exp Med 201: 647-657; Takahashi, K et al., (2007) PLoS Med 4: e124; and Hsieh, CL et al., (2009) J Neurochem 109: 1144-1156; Malm, TM et al, *Neurotherapeutics*. 2014 Nov 18; Paloneva, J et al., (2002) Am J Hum Genet 71: 656-662; and Paloneva, J et al., (2003) J Exp Med 198: 669-675; Guerreiro, RJ et al., (2013) JAMA Neurol 70: 78-84; Guerreiro, RJ et al., (2012) Arch Neurol: 1-7; Guerreiro, R et al., (2013) N Engl J Med 368: 117-127; Jonsson, T et al., (2013) N Engl J Med 368: 107-116; and Neumann, H et al., (2013) N Engl J Med 368: 182-184; and Wang Y, Cell. 2015;160(6):1061-71).

[0006] Accordingly, there is a need for therapeutic anti-TREM2 antibodies to treat diseases, disorders, and conditions associated with decreased TREM2 activity.

[0007] All references cited herein, including patent applications and publications, are hereby incorporated by reference in their entirety.

SUMMARY

[0008] The present disclosure is generally directed to compositions that include antibodies, *e.g.*, monoclonal, chimeric, humanized antibodies, antibody fragments, *etc.*, that specifically bind a

TREM2 protein, *e.g.*, a mammalian TREM2 (*e.g.*, any non-human mammal) or human TREM2, and to methods of using such compositions.

[0009] Certain examples of the present disclosure are based, at least in part, on the identification of anti-TREM2 antibodies with improved affinity and functional characteristics. Surprisingly, the functional characteristics of the anti-TREM2 antibodies were not predictable from the increase in affinity. In some examples, anti-TREM2 antibodies of the present disclosure bind both human and cynomolgus monkey TREM2 with an affinity that is at least about 1-fold higher than an anti-TREM2 antibody selected from anti-TREM2 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 27 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 56 (*e.g.*, antibody AL2p-h50); an anti-TREM2 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 91 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 103 (*e.g.*, antibody AL2p-h77); and an anti-TREM2 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 119 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 120 (*e.g.*, antibody AL2). In some examples, anti-TREM2 antibodies of the present disclosure bind to primary human immune cells with an affinity that is at least about 10 times higher than that of an anti-TREM2 antibody selected from an anti-TREM2 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 27 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 56; an anti-TREM2 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 91 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 103; and an anti-TREM2 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 119 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 120. In some examples, anti-TREM2 antibodies of the present disclosure cluster and activate TREM2 signaling in an amount that is at least about 1-fold greater than that of an anti-TREM2 antibody selected from an anti-TREM2 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 27 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 56; an anti-TREM2 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 91 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 103; and an anti-TREM2 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 119 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 120. In some examples, anti-TREM2 antibodies of the present disclosure increase immune cell survival *in vitro* that to an extent that is greater than an anti-TREM2 antibody selected from an anti-TREM2 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 27 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 56; an anti-TREM2 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 91 and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 103; and an anti-TREM2 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 119 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 120. In some examples, anti-TREM2 antibodies of the present disclosure may also have improved *in vivo* half-lives. In some examples, anti-TREM2 antibodies of the present disclosure may also decrease plasma levels of soluble TREM2 *in vivo*. In some examples, anti-TREM2 antibodies of the present disclosure may also decrease soluble TREM2. In some examples, the soluble TREM2 is decreased about any of 10, 20, 30, 40, 50 or 60%.

[0010] Accordingly, certain examples of the present disclosure relate to an antibody that binds to a TREM2 protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising the sequence according to Formula I: YAFX₁X₂X₃WMN, wherein X₁ is S or W, X₂ is S, L, or R, and X₃ is S, D, H, Q, or E (SEQ ID NO: 121); an HVR-H2 comprising the sequence according to Formula II: RIYPGX₁GX₂TNYAX₃KX₄X₅G, wherein X₁ is D, G, E, Q, or V, X₂ is D or Q, X₃ is Q, R, H, W, Y, or G, X₄ is F, R, or W, and X₅ is Q, R, K, or H (SEQ ID NO: 122); and an HVR-H3 comprising the sequence according to Formula III: ARLLRNX₁PGX₂SYAX₃DY, wherein X₁ is Q or K, X₂ is E, S, or A, and X₃ is M or H (SEQ ID NO: 123), and wherein the antibody is not an antibody comprising a heavy chain variable region comprising an HVR-H1 comprising the sequence of YAFSSSWMN (SEQ ID NO: 124), an HVR-H2 comprising the sequence of RIYPGDGDTNYAQKFQG (SEQ ID NO: 125), and an HVR-H3 comprising the sequence of ARLLRNQPGESYAMDY (SEQ ID NO: 126). Other examples of the present disclosure relate to an antibody that binds to a TREM2 protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the light chain variable region comprises: an HVR-L1 comprising the sequence according to Formula IV: RX₁SX₂SLX₃HSNX₄YTYLH, wherein X₁ is S or T, X₂ is Q, R, or S, X₃ is V or I, and X₄ is G, R, W, Q, or A (SEQ ID NO: 127); an HVR-L2 comprising the sequence according to Formula V: KVSNRX₁S, wherein X₁ is F, R, V, or K (SEQ ID NO: 128); and an HVR-L3 comprising the sequence according to Formula V: SQSTRVPYT (SEQ ID NO: 129), and wherein the antibody is not an antibody comprising a light chain variable region comprising an HVR-L1 comprising the sequence of RSSQSLVHSNGYTYLH (SEQ ID NO: 130), an HVR-L2 comprising the sequence of KVSNRFS (SEQ ID NO: 131), and an HVR-L3 comprising the sequence of SQSTRVPYT (SEQ ID NO: 129). Other examples of the present disclosure relate to an antibody that binds to a TREM2 protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising the sequence according to Formula I: YAFX₁X₂X₃WMN, wherein X₁ is S or W, X₂ is S, L, or R, and X₃ is S, D, H, Q, or E (SEQ ID NO: 121); an HVR-H2 comprising the sequence according to Formula II: RIYPGX₁GX₂TNYAX₃KX₄X₅G, wherein X₁ is D, G, E, Q, or V, X₂ is D or Q, X₃ is Q, R, H, W, Y, or G, X₄ is F, R, or W, and X₅ is Q, R, K, or H (SEQ ID NO: 122); and an HVR-H3 comprising the

sequence according to Formula III: ARLLRN_{X1}PGX₂SYAX₃DY, wherein X₁ is Q or K, X₂ is E, S, or A, and X₃ is M or H (SEQ ID NO: 123), and the light chain variable region comprises: an HVR-L1 comprising the sequence according to Formula IV: RX₁SX₂SLX₃HSNX₄YTYLH, wherein X₁ is S or T, X₂ is Q, R, or S, X₃ is V or I, and X₄ is G, R, W, Q, or A (SEQ ID NO: 127); an HVR-L2 comprising the sequence according to Formula V: KVSNRX₁S, wherein X₁ is F, R, V, or K (SEQ ID NO: 128); and an HVR-L3 comprising the sequence: SQSTRVPYT (SEQ ID NO: 129), and wherein the antibody is not an antibody comprising a heavy chain variable region comprising an HVR-H1 comprising the sequence of YAFSSSWMN (SEQ ID NO: 124), an HVR-H2 comprising the sequence of RIYPGDGDTNYAQKFQG (SEQ ID NO: 125), and an HVR-H3 comprising the sequence of ARLLRNQPGESYAMDY (SEQ ID NO: 126), and comprising a light chain variable region comprising an HVR-L1 comprising the sequence of RSSQSLVHSNGYTYLH (SEQ ID NO: 130), an HVR-L2 comprising the sequence of KVSNRFS (SEQ ID NO: 131), and an HVR-L3 comprising the sequence of SQSTRVPYT (SEQ ID NO: 129).

[0011] Other examples of the present disclosure relate to an antibody that binds to a TREM2 protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising a sequence selected from the group consisting of SEQ ID Nos: 132 and 136; an HVR-H2 comprising a sequence selected from the group consisting of SEQ ID Nos: 133, 135, 137, and 141; and an HVR-H3 comprising a sequence selected from the group consisting of SEQ ID Nos: 126 and 138; and/or the light the light chain variable region comprises: an HVR-L1 comprising a sequence selected from the group consisting of 130, 139, 142, and 144; an HVR-L2 comprising a sequence selected from the group consisting of SEQ ID Nos: 131, 134, and 140; and an HVR-L3 comprising the sequence of SEQ ID NO: 129. Other examples of the present disclosure relate to an antibody that binds to a TREM2 protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising the sequence of SEQ ID No: 132; an HVR-H2 comprising a sequence selected from the group consisting of SEQ ID Nos: 133, 135, and 141; and an HVR-H3 comprising the sequence of SEQ ID No: 126; and/or the light the light chain variable region comprises: an HVR-L1 comprising a sequence selected from the group consisting of 130, 142, and 144; an HVR-L2 comprising a sequence selected from the group consisting of SEQ ID Nos: 131 and 134; and an HVR-L3 comprising the sequence of SEQ ID NO: 129.

[0012] Other examples of the present disclosure relate to an antibody that binds to a TREM2 protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the HVR-H1, HVR-H2, and HVR-H3 of antibody AL2p-2, AL2p-3, AL2p-4, AL2p-7, AL2p-8, AL2p-9, AL2p-10, AL2p-11, AL2p-12, AL2p-13, AL2p-14, AL2p-15, AL2p-16, AL2p-17, AL2p-18, AL2p-19, AL2p-20, AL2p-21, AL2p-22, AL2p-23, AL2p-24, AL2p-25, AL2p-26, AL2p-27, AL2p-28, AL2p-29, AL2p-30, AL2p-31, AL2p-

32, AL2p-35, AL2p-36, AL2p-37, AL2p-38, AL2p-39, AL2p-40, AL2p-41, AL2p-42, AL2p-43, AL2p-44, AL2p-45, AL2p-46, AL2p-47, AL2p-48, AL2p-49, AL2p-50, AL2p-51, AL2p-52, AL2p-53, AL2p-54, AL2p-55, AL2p-56, AL2p-57, AL2p-58, AL2p-59, AL2p-60, AL2p-61, or AL2p-62 (as shown in Tables 2A to 2C). Other examples of the present disclosure relate to an antibody that binds to a TREM2 protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the light chain variable region comprises the HVR-L1, HVR-L2, and HVR-L3 of antibody AL2p-5, AL2p-6, AL2p-7, AL2p-8, AL2p-9, AL2p-10, AL2p-11, AL2p-12, AL2p-13, AL2p-14, AL2p-15, AL2p-16, AL2p-17, AL2p-18, AL2p-19, AL2p-20, AL2p-21, AL2p-22, AL2p-23, AL2p-24, AL2p-25, AL2p-26, AL2p-27, AL2p-28, AL2p-29, AL2p-30, AL2p-31, AL2p-32, AL2p-33, AL2p-38, AL2p-39, AL2p-40, AL2p-41, AL2p-42, AL2p-43, AL2p-44, AL2p-45, AL2p-46, AL2p-47, AL2p-48, AL2p-49, AL2p-50, AL2p-51, AL2p-52, AL2p-53, AL2p-54, AL2p-55, AL2p-56, AL2p-57, AL2p-58, AL2p-59, AL2p-60, AL2p-61, or AL2p-62 (as shown in Tables 3A to 3C). Other examples of the present disclosure relate to an antibody that binds to a TREM2 protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the HVR-H1, HVR-H2, and HVR-H3 of antibody AL2p-2, AL2p-3, AL2p-4, AL2p-7, AL2p-8, AL2p-9, AL2p-10, AL2p-11, AL2p-12, AL2p-13, AL2p-14, AL2p-15, AL2p-16, AL2p-17, AL2p-18, AL2p-19, AL2p-20, AL2p-21, AL2p-22, AL2p-23, AL2p-24, AL2p-25, AL2p-26, AL2p-27, AL2p-28, AL2p-29, AL2p-30, AL2p-31, AL2p-32, AL2p-35, AL2p-36, AL2p-37, AL2p-38, AL2p-39, AL2p-40, AL2p-41, AL2p-42, AL2p-43, AL2p-44, AL2p-45, AL2p-46, AL2p-47, AL2p-48, AL2p-49, AL2p-50, AL2p-51, AL2p-52, AL2p-53, AL2p-54, AL2p-55, AL2p-56, AL2p-57, AL2p-58, AL2p-59, AL2p-60, AL2p-61, or AL2p-62 (as shown in Tables 2A to 2C); and the light chain variable region comprises the HVR-L1, HVR-L2, and HVR-L3 of antibody AL2p-5, AL2p-6, AL2p-7, AL2p-8, AL2p-9, AL2p-10, AL2p-11, AL2p-12, AL2p-13, AL2p-14, AL2p-15, AL2p-16, AL2p-17, AL2p-18, AL2p-19, AL2p-20, AL2p-21, AL2p-22, AL2p-23, AL2p-24, AL2p-25, AL2p-26, AL2p-27, AL2p-28, AL2p-29, AL2p-30, AL2p-31, AL2p-32, AL2p-33, AL2p-38, AL2p-39, AL2p-40, AL2p-41, AL2p-42, AL2p-43, AL2p-44, AL2p-45, AL2p-46, AL2p-47, AL2p-48, AL2p-49, AL2p-50, AL2p-51, AL2p-52, AL2p-53, AL2p-54, AL2p-55, AL2p-56, AL2p-57, AL2p-58, AL2p-59, AL2p-60, AL2p-61, or AL2p-62 (as shown in Tables 3A to 3C). Other examples of the present disclosure relate to an antibody that binds to a TREM2 protein, wherein the antibody comprises a heavy chain variable region comprising an HVR-H1, HVR-H2, and HVR-H3 and a light chain variable region comprising an HVR-L1, HVR-L2, and HVR-L3, wherein the antibody comprises the HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2, and HVR-L3 of antibody AL2p-2, AL2p-3, AL2p-4, AL2p-5, AL2p-6, AL2p-7, AL2p-8, AL2p-9, AL2p-10, AL2p-11, AL2p-12, AL2p-13, AL2p-14, AL2p-15, AL2p-16, AL2p-17, AL2p-18, AL2p-19, AL2p-20, AL2p-21, AL2p-22, AL2p-23, AL2p-24, AL2p-25, AL2p-26, AL2p-27, AL2p-28, AL2p-29, AL2p-30, AL2p-31, AL2p-32, AL2p-33, AL2p-35, AL2p-36, AL2p-37, AL2p-38, AL2p-39, AL2p-40, AL2p-41, AL2p-42, AL2p-43, AL2p-44, AL2p-45, AL2p-46, AL2p-47, AL2p-48, AL2p-49, AL2p-

50, AL2p-51, AL2p-52, AL2p-53, AL2p-54, AL2p-55, AL2p-56, AL2p-57, AL2p-58, AL2p-59, AL2p-60, AL2p-61, or AL2p-62 (as shown in Tables 2A to 2C and 3A to 3C).

[0013] In some examples that may be combined with any of the preceding examples, the heavy chain variable region comprises one, two, three or four frame work regions selected from VH FR1, VH FR2, VH FR3, and VH FR4, wherein: the VH FR1 comprises a sequence selected from the group consisting of SEQ ID NOs: 9-11, the VH FR2 comprises a sequence selected from the group consisting of SEQ ID NOs: 12 and 13, the VH FR3 comprises a sequence selected from the group consisting of SEQ ID NOs: 14 and 15, and the VH FR4 comprises the sequence of SEQ ID NO: 16; and/or the light chain variable region comprises one, two, three or four frame work regions selected from VL FR1, VL FR2, VL FR3, and VL FR4, wherein: the VL FR1 comprises a sequence selected from the group consisting of SEQ ID NOs: 17-20, the VL FR2 comprises a sequence selected from the group consisting of SEQ ID NOs: 21 and 22, the VL FR3 comprises a sequence selected from the group consisting of SEQ ID NOs: 23 and 24, and the VL FR4 comprises a sequence selected from the group consisting of SEQ ID NOs: 25 and 26. In some examples that may be combined with any of the preceding examples, the antibody comprises a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 27-71 and 91; and/or a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 92-113 and 118. In some examples that may be combined with any of the preceding examples, the antibody comprises the heavy chain variable region of antibody AL2p-h50, AL2p-2, AL2p-3, AL2p-4, AL2p-5, AL2p-6, AL2p-7, AL2p-8, AL2p-9, AL2p-10, AL2p-11, AL2p-12, AL2p-13, AL2p-14, AL2p-15, AL2p-16, AL2p-17, AL2p-18, AL2p-19, AL2p-20, AL2p-21, AL2p-22, AL2p-23, AL2p-24, AL2p-25, AL2p-26, AL2p-27, AL2p-28, AL2p-29, AL2p-30, AL2p-31, AL2p-32, AL2p-33, AL2p-h77, AL2p-35, AL2p-36, AL2p-37, AL2p-38, AL2p-39, AL2p-40, AL2p-41, AL2p-42, AL2p-43, AL2p-44, AL2p-45, AL2p-46, AL2p-47, AL2p-48, AL2p-49, AL2p-50, AL2p-51, AL2p-52, AL2p-53, AL2p-54, AL2p-55, AL2p-56, AL2p-57, AL2p-58, AL2p-59, AL2p-60, AL2p-61, or AL2p-62 (as shown in Table 6A); and/or the antibody comprises the light chain variable region of antibody AL2p-h50, AL2p-2, AL2p-3, AL2p-4, AL2p-5, AL2p-6, AL2p-7, AL2p-8, AL2p-9, AL2p-10, AL2p-11, AL2p-12, AL2p-13, AL2p-14, AL2p-15, AL2p-16, AL2p-17, AL2p-18, AL2p-19, AL2p-20, AL2p-21, AL2p-22, AL2p-23, AL2p-24, AL2p-25, AL2p-26, AL2p-27, AL2p-28, AL2p-29, AL2p-30, AL2p-31, AL2p-32, AL2p-33, AL2p-h77, AL2p-35, AL2p-36, AL2p-37, AL2p-38, AL2p-39, AL2p-40, AL2p-41, AL2p-42, AL2p-43, AL2p-44, AL2p-45, AL2p-46, AL2p-47, AL2p-48, AL2p-49, AL2p-50, AL2p-51, AL2p-52, AL2p-53, AL2p-54, AL2p-55, AL2p-56, AL2p-57, AL2p-58, AL2p-59, AL2p-60, AL2p-61, or AL2p-62 (as shown in Table 7A). In some examples that may be combined with any of the preceding examples: (a) the HVR-H1 comprises the amino acid sequence YAFSSQWMN (SEQ ID NO: 132), the HVR-H2 comprises the amino acid sequence RIYPGGGDTNYARKFQG (SEQ ID NO: 133), the HVR-H3 comprises the amino acid sequence ARLLRNQPGESYAMDY (SEQ ID NO: 126), the HVR-L1 comprises the

amino acid sequence RSSQSLVHSNGYTYLH (SEQ ID NO: 130), the HVR-L2 comprises the amino acid sequence KVSNNRRS (SEQ ID NO: 134), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 129); (b) the HVR-H1 comprises the amino acid sequence YAFSSQWMN (SEQ ID NO: 132), the HVR-H2 comprises the amino acid sequence RIYPGGGDTNYAGKFQG (SEQ ID NO: 135), the HVR-H3 comprises the amino acid sequence ARLLRNQPGESYAMDY (SEQ ID NO: 126), the HVR-L1 comprises the amino acid sequence RSSQSLVHSNGYTYLH (SEQ ID NO: 130), the HVR-L2 comprises the amino acid sequence KVSNNRFS (SEQ ID NO: 131), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 129); (c) the HVR-H1 comprises the amino acid sequence YAFSSDWMN (SEQ ID NO: 136), the HVR-H2 comprises the amino acid sequence RIYPGEGDTNYARKFHG (SEQ ID NO: 137), the HVR-H3 comprises the amino acid sequence ARLLRNKPGESYAMDY (SEQ ID NO: 138), the HVR-L1 comprises the amino acid sequence RTSQSLVHSNAYTYLH (SEQ ID NO: 139), the HVR-L2 comprises the amino acid sequence KVSNNRVS (SEQ ID NO: 140), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 129); (d) the HVR-H1 comprises the amino acid sequence YAFSSQWMN (SEQ ID NO: 132), the HVR-H2 comprises the amino acid sequence RIYPGEGDTNYARKFQG (SEQ ID NO: 141), the HVR-H3 comprises the amino acid sequence ARLLRNQPGESYAMDY (SEQ ID NO: 126), the HVR-L1 comprises the amino acid sequence RSSQSLVHSNQYTYLH (SEQ ID NO: 142), the HVR-L2 comprises the amino acid sequence KVSNNRRS (SEQ ID NO: 134), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 129); (e) the HVR-H1 comprises the amino acid sequence YAFSSQWMN (SEQ ID NO: 132), the HVR-H2 comprises the amino acid sequence RIYPGEGDTNYAGKFQG (SEQ ID NO: 143), the HVR-H3 comprises the amino acid sequence ARLLRNQPGESYAMDY (SEQ ID NO: 126), the HVR-L1 comprises the amino acid sequence RSSQSLVHSNQYTYLH (SEQ ID NO: 142), the HVR-L2 comprises the amino acid sequence KVSNNRFS (SEQ ID NO: 131), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 129); (f) the HVR-H1 comprises the amino acid sequence YAFSSQWMN (SEQ ID NO: 132), the HVR-H2 comprises the amino acid sequence RIYPGGGDTNYAGKFQG (SEQ ID NO: 135), the HVR-H3 comprises the amino acid sequence ARLLRNQPGESYAMDY (SEQ ID NO: 126), the HVR-L1 comprises the amino acid sequence RSSQSLVHSNRYTYLH (SEQ ID NO: 144), the HVR-L2 comprises the amino acid sequence KVSNNRFS (SEQ ID NO: 131), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 129); or (g) the HVR-H1 comprises the amino acid sequence YAFSSQWMN (SEQ ID NO: 132), the HVR-H2 comprises the amino acid sequence RIYPGGGDTNYARKFQG (SEQ ID NO: 133), the HVR-H3 comprises the amino acid sequence ARLLRNQPGESYAMDY (SEQ ID NO: 126), the HVR-L1 comprises the amino acid sequence RSSQSLVHSNRYTYLH (SEQ ID NO: 144), the HVR-L2 comprises the amino acid sequence KVSNNRRS (SEQ ID NO: 134), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 129). In some examples that may be combined with any of the

preceding examples, the HVR-H1 comprises the amino acid sequence YAFSSQWMN (SEQ ID NO: 132), the HVR-H2 comprises the amino acid sequence RIYPGGGDTNYARKFQG (SEQ ID NO: 133), the HVR-H3 comprises the amino acid sequence ARLLRNQPGESYAMDY (SEQ ID NO: 126), the HVR-L1 comprises the amino acid sequence RSSQSLVHSNGYTYLH (SEQ ID NO: 130), the HVR-L2 comprises the amino acid sequence KVSNNRRS (SEQ ID NO: 134), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 129). In some examples that may be combined with any of the preceding examples, the HVR-H1 comprises the amino acid sequence YAFSSQWMN (SEQ ID NO: 132), the HVR-H2 comprises the amino acid sequence RIYPGGGDTNYAGKFQG (SEQ ID NO: 135), the HVR-H3 comprises the amino acid sequence ARLLRNQPGESYAMDY (SEQ ID NO: 126), the HVR-L1 comprises the amino acid sequence RSSQSLVHSNGYTYLH (SEQ ID NO: 130), the HVR-L2 comprises the amino acid sequence KVSNNRFS (SEQ ID NO: 131), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 129). In some examples that may be combined with any of the preceding examples, the HVR-H1 comprises the amino acid sequence YAFSSDWMN (SEQ ID NO: 136), the HVR-H2 comprises the amino acid sequence RIYPGEGDTNYARKFHG (SEQ ID NO: 137), the HVR-H3 comprises the amino acid sequence ARLLRNKPGESYAMDY (SEQ ID NO: 138), the HVR-L1 comprises the amino acid sequence RTSQSLVHSNAYTYLH (SEQ ID NO: 139), the HVR-L2 comprises the amino acid sequence KVSNNRVS (SEQ ID NO: 140), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 129). In some examples that may be combined with any of the preceding examples, the HVR-H1 comprises the amino acid sequence YAFSSQWMN (SEQ ID NO: 132), the HVR-H2 comprises the amino acid sequence RIYPGEGDTNYARKFQG (SEQ ID NO: 141), the HVR-H3 comprises the amino acid sequence ARLLRNQPGESYAMDY (SEQ ID NO: 126), the HVR-L1 comprises the amino acid sequence RSSQSLVHSNQYTYLH (SEQ ID NO: 142), the HVR-L2 comprises the amino acid sequence KVSNNRRS (SEQ ID NO: 134), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 129). In some examples that may be combined with any of the preceding examples, the HVR-H1 comprises the amino acid sequence YAFSSQWMN (SEQ ID NO: 132), the HVR-H2 comprises the amino acid sequence RIYPGEGDTNYAGKFQG (SEQ ID NO: 143), the HVR-H3 comprises the amino acid sequence ARLLRNQPGESYAMDY (SEQ ID NO: 126), the HVR-L1 comprises the amino acid sequence RSSQSLVHSNQYTYLH (SEQ ID NO: 142), the HVR-L2 comprises the amino acid sequence KVSNNRFS (SEQ ID NO: 131), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 129). In some examples that may be combined with any of the preceding examples, the HVR-H1 comprises the amino acid sequence YAFSSQWMN (SEQ ID NO: 132), the HVR-H2 comprises the amino acid sequence RIYPGGGDTNYAGKFQG (SEQ ID NO: 135), the HVR-H3 comprises the amino acid sequence ARLLRNQPGESYAMDY (SEQ ID NO: 126), the HVR-L1 comprises the amino acid sequence RSSQSLVHSNRYTYLH (SEQ ID NO: 144), the HVR-L2 comprises the amino acid sequence

KVSNRFS (SEQ ID NO: 131), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 129). In some examples that may be combined with any of the preceding examples, the HVR-H1 comprises the amino acid sequence YAFSSQWMN (SEQ ID NO: 132), the HVR-H2 comprises the amino acid sequence RIYPGGGDTNYARKFQG (SEQ ID NO: 133), the HVR-H3 comprises the amino acid sequence ARLLRNQPGESYAMDY (SEQ ID NO: 126), the HVR-L1 comprises the amino acid sequence RSSQSLVHSNRYTYLH (SEQ ID NO: 144), the HVR-L2 comprises the amino acid sequence KVSNNRS (SEQ ID NO: 134), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 129). In some examples, the HVR-H1 comprises the amino acid sequence YAFSSQWMN (SEQ ID NO: 132), the HVR-H2 comprises the amino acid sequence RIYPGGGDTNYAGKFQG (SEQ ID NO: 135), the HVR-H3 comprises the amino acid sequence ARLLRNQPGESYAMDY (SEQ ID NO: 126), the HVR-L1 comprises the amino acid sequence RSSQSLVHSNRYTYLH (SEQ ID NO: 144), the HVR-L2 comprises the amino acid sequence KVSNNRS (SEQ ID NO: 131), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 129).

[0014] Other examples of the present disclosure relate to an antibody that binds to a TREM2 protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises Kabat CDRs; and/or the light chain variable region comprises Kabat CDRs. In some examples, the heavy chain variable region comprises a CDR-H1 comprising the sequence of SQWMN (SEQ ID NO: 194), a CDR-H2 comprising the sequence of RIYPGGGDTNYAGKFQG (SEQ ID NO: 135); and a CDR-H3 comprising the sequence of LLRNQPGESYAMDY (SEQ ID NO: 195). In some examples, the light chain variable region comprises a CDR-L1 comprising the sequence of RSSQSLVHSNGYTYLH (SEQ ID NO: 130), a CDR-L2 comprising the sequence of KVSNNRS (SEQ ID NO: 131); and a CDR-L3 comprising the sequence of SQSTRVPYT (SEQ ID NO: 129). In some examples, the heavy chain variable region comprises a CDR-H1 comprising the sequence of SQWMN (SEQ ID NO: 194), a CDR-H2 comprising the sequence of RIYPGGGDTNYAGKFQG (SEQ ID NO: 135); and a CDR-H3 comprising the sequence of LLRNQPGESYAMDY (SEQ ID NO: 195); and the light chain variable region comprises a CDR-L1 comprising the sequence of RSSQSLVHSNGYTYLH (SEQ ID NO: 130), a CDR-L2 comprising the sequence of KVSNNRS (SEQ ID NO: 131); and a CDR-L3 comprising the sequence of SQSTRVPYT (SEQ ID NO: 129).

[0015] Other examples of the present disclosure relate to an antibody that binds to a TREM2 protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises Kabat CDRs; and/or the light chain variable region comprises Kabat CDRs. In some examples, the heavy chain variable region comprises a CDR-H1 comprising the sequence of SDWMN (SEQ ID NO: 196), a CDR-H2 comprising the sequence of RIYPGEGDTNYARKFHG (SEQ ID NO: 137); and a CDR-H3 comprising the sequence of LLRNKPGESYAMDY (SEQ ID NO: 197). In some examples, the

light chain variable region comprises a CDR-L1 comprising the sequence of RTSQSLVHSNAYTYLH (SEQ ID NO: 139), a CDR-L2 comprising the sequence of KVSNRVS (SEQ ID NO: 140); and a CDR-L3 comprising the sequence of SQSTRVPYT (SEQ ID NO: 129). In some examples, the heavy chain variable region comprises a CDR-H1 comprising the sequence of SDWMN (SEQ ID NO: 196), a CDR-H2 comprising the sequence of RIYPGGGDTNYARKFHG (SEQ ID NO: 137); and a CDR-H3 comprising the sequence of LLRNKPGESYAMDY (SEQ ID NO: 197); and the light chain variable region comprises a CDR-L1 comprising the sequence of RTSQSLVHSNAYTYLH (SEQ ID NO: 139), a CDR-L2 comprising the sequence of KVSNRVS (SEQ ID NO: 140); and a CDR-L3 comprising the sequence of SQSTRVPYT (SEQ ID NO: 129).

[0016] Other examples of the present disclosure relate to an antibody that binds to a TREM2 protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises Kabat CDRs; and/or the light chain variable region comprises Kabat CDRs. In some examples, the heavy chain variable region comprises a CDR-H1 comprising the sequence of SQWMN (SEQ ID NO: 194), a CDR-H2 comprising the sequence of RIYPGGGDTNYAGKFQG (SEQ ID NO: 135); and a CDR-H3 comprising the sequence of LLRNQPGESYAMDY (SEQ ID NO: 195). In some examples, the light chain variable region comprises a CDR-L1 comprising the sequence of RSSQSLVHSNRYTYLH (SEQ ID NO: 144), a CDR-L2 comprising the sequence of KVSNRFS (SEQ ID NO: 131); and a CDR-L3 comprising the sequence of SQSTRVPYT (SEQ ID NO: 129). In some examples, the heavy chain variable region comprises a CDR-H1 comprising the sequence of SQWMN (SEQ ID NO: 194), a CDR-H2 comprising the sequence of RIYPGGGDTNYAGKFQG (SEQ ID NO: 135); and a Kabat CDR-H3 comprising the sequence of LLRNQPGESYAMDY (SEQ ID NO: 195); and the light chain variable region comprises a CDR-L1 comprising the sequence of RSSQSLVHSNRYTYLH (SEQ ID NO: 144), a CDR-L2 comprising the sequence of KVSNRFS (SEQ ID NO: 131); and a CDR-L3 comprising the sequence of SQSTRVPYT (SEQ ID NO: 129).

[0017] Other examples of the present disclosure relate to an antibody that binds to a TREM2 protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises Kabat CDRs; and/or the light chain variable region comprises Kabat CDRs. In some examples, the heavy chain variable region comprises a CDR-H1 comprising the sequence of SQWMN (SEQ ID NO: 194), a CDR-H2 comprising the sequence of RIYPGGGDTNYARKFQG (SEQ ID NO: 133); and a CDR-H3 comprising the sequence of LLRNQPGESYAMDY (SEQ ID NO: 195). In some examples, the light chain variable region comprises a CDR-L1 comprising the sequence of RSSQSLVHSNRYTYLH (SEQ ID NO: 144), a CDR-L2 comprising the sequence of KVSNRFS (SEQ ID NO: 131); and a CDR-L3 comprising the sequence of SQSTRVPYT (SEQ ID NO: 129). In some examples, the heavy chain variable region comprises a CDR-H1 comprising the sequence of SQWMN (SEQ ID NO: 194), a CDR-H2 comprising the sequence of RIYPGGGDTNYARKFQG

(SEQ ID NO: 133); and a CDR-H3 comprising the sequence of LLRNQPGESYAMDY (SEQ ID NO: 195); and the light chain variable region comprises a CDR-L1 comprising the sequence of RSSQSLVHSNRYTYLH (SEQ ID NO: 144), a CDR-L2 comprising the sequence of KVSNNRRS (SEQ ID NO: 134); and a CDR-L3 comprising the sequence of SQSTRVPYT (SEQ ID NO: 129).

[0018] Other examples of the present disclosure relate to an antibody that binds to a TREM2 protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises Kabat CDRs; and/or the light chain variable region comprises Kabat CDRs. In some examples, the heavy chain variable region comprises a CDR-H1 comprising the sequence of SQWMN (SEQ ID NO: 194), a CDR-H2 comprising the sequence of RIYPGEGDTNYARKFQG (SEQ ID NO: 141); and a CDR-H3 comprising the sequence of LLRNQPGESYAMDY (SEQ ID NO: 195). In some examples, the light chain variable region comprises a CDR-L1 comprising the sequence of RSSQSLVHSNQYTYLH (SEQ ID NO: 142), a CDR-L2 comprising the sequence of KVSNNRRS (SEQ ID NO: 134); and a CDR-L3 comprising the sequence of SQSTRVPYT (SEQ ID NO: 129). In some examples, the heavy chain variable region comprises a CDR-H1 comprising the sequence of SQWMN (SEQ ID NO: 194), a CDR-H2 comprising the sequence of RIYPGEGDTNYARKFQG (SEQ ID NO: 141); and a CDR-H3 comprising the sequence of LLRNQPGESYAMDY (SEQ ID NO: 195); and the light chain variable region comprises a CDR-L1 comprising the sequence of RSSQSLVHSNQYTYLH (SEQ ID NO: 142), a CDR-L2 comprising the sequence of KVSNNRRS (SEQ ID NO: 134); and a CDR-L3 comprising the sequence of SQSTRVPYT (SEQ ID NO: 129).

[0019] Other examples of the present disclosure relate to an antibody that binds to a TREM2 protein, wherein the antibody comprises a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 27-71 and 91; and/or a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 92-113 and 118. In some examples, the antibody comprises the heavy chain variable region of antibody AL2p-h50, AL2p-2, AL2p-3, AL2p-4, AL2p-5, AL2p-6, AL2p-7, AL2p-8, AL2p-9, AL2p-10, AL2p-11, AL2p-12, AL2p-13, AL2p-14, AL2p-15, AL2p-16, AL2p-17, AL2p-18, AL2p-19, AL2p-20, AL2p-21, AL2p-22, AL2p-23, AL2p-24, AL2p-25, AL2p-26, AL2p-27, AL2p-28, AL2p-29, AL2p-30, AL2p-31, AL2p-32, AL2p-33, AL2p-h77, AL2p-35, AL2p-36, AL2p-37, AL2p-38, AL2p-39, AL2p-40, AL2p-41, AL2p-42, AL2p-43, AL2p-44, AL2p-45, AL2p-46, AL2p-47, AL2p-48, AL2p-49, AL2p-50, AL2p-51, AL2p-52, AL2p-53, AL2p-54, AL2p-55, AL2p-56, AL2p-57, AL2p-58, AL2p-59, AL2p-60, AL2p-61, or AL2p-62 (as shown in Table 6A); and/or the antibody comprises the light chain variable region of antibody AL2p-h50, AL2p-2, AL2p-3, AL2p-4, AL2p-5, AL2p-6, AL2p-7, AL2p-8, AL2p-9, AL2p-10, AL2p-11, AL2p-12, AL2p-13, AL2p-14, AL2p-15, AL2p-16, AL2p-17, AL2p-18, AL2p-19, AL2p-20, AL2p-21, AL2p-22, AL2p-23, AL2p-24, AL2p-25, AL2p-26, AL2p-27, AL2p-28, AL2p-29, AL2p-30, AL2p-31, AL2p-32, AL2p-33, AL2p-h77, AL2p-35, AL2p-36, AL2p-37, AL2p-38, AL2p-39, AL2p-40, AL2p-41, AL2p-42, AL2p-43, AL2p-

44, AL2p-45, AL2p-46, AL2p-47, AL2p-48, AL2p-49, AL2p-50, AL2p-51, AL2p-52, AL2p-53, AL2p-54, AL2p-55, AL2p-56, AL2p-57, AL2p-58, AL2p-59, AL2p-60, AL2p-61, or AL2p-62 (as shown in Table 7A). In some examples: (a) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 53, and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO: 97; (b) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 59; and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO: 104; (c) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 64; and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO: 108; (d) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 70; and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO: 110; (e) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 71; and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO: 111; (f) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 59; and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO: 112; or (g) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 53; and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO: 113. In some examples, the antibody comprises an Fc region comprising an amino acid sequence selected from the group consisting of SEQ ID Nos: 146-156. In some examples, the antibody comprises an Fc region comprising the amino acid sequence of SEQ ID NO: 146. In some examples, the antibody comprises an Fc region comprising the amino acid sequence of SEQ ID NO: 147. In some examples, the antibody comprises an Fc region comprising the amino acid sequence of SEQ ID NO: 148. In some examples, the antibody comprises an Fc region comprising the amino acid sequence of SEQ ID NO: 149. In some examples, the antibody comprises an Fc region comprising the amino acid sequence of SEQ ID NO: 150. In some examples, the antibody comprises an Fc region comprising the amino acid sequence of SEQ ID NO: 151. In some examples, the antibody comprises an Fc region comprising the amino acid sequence of SEQ ID NO: 152. In some examples, the antibody comprises an Fc region comprising the amino acid sequence of SEQ ID NO: 153. In some examples, the antibody comprises an Fc region comprising the amino acid sequence of SEQ ID NO: 154. In some examples, the antibody comprises an Fc region comprising the amino acid sequence of SEQ ID NO: 155. In some examples, the antibody comprises an Fc region comprising the amino acid sequence of SEQ ID NO: 156. In some examples, the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 198-213; and/or a light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 214-218. In some examples, the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 198 and 199; and a light chain comprising the amino acid sequence of SEQ ID NO: 214. In some examples, the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of

SEQ ID NOs: 200 and 201; and a light chain comprising the amino acid sequence of SEQ ID NO: 214. In some examples, the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 202 and 203; and a light chain comprising the amino acid sequence of SEQ ID NO: 215. In some examples, the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 204 and 205; and a light chain comprising the amino acid sequence of SEQ ID NO: 215. In some examples, the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 206 and 207; and a light chain comprising the amino acid sequence of SEQ ID NO: 216. In some examples, the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 208 and 209; and a light chain comprising the amino acid sequence of SEQ ID NO: 218. In some examples, the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 210 and 211; and a light chain comprising the amino acid sequence of SEQ ID NO: 218. In some examples, the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 212 and 213; and a light chain comprising the amino acid sequence of SEQ ID NO: 217.

[0020] In some examples, the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 53, and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO: 97. In some examples, the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 59; and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO: 104. In some examples, the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 64; and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO: 108. In some examples, the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 70; and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO: 110. In some examples, the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 71; and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO: 11. In some examples, the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 59; and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO: 112. In some examples, the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 53; and/or the light chain variable region comprises the amino acid sequence of SEQ ID NO: 113.

[0021] Other examples of the present disclosure relate to an antibody that binds to a TREM2 protein, wherein the antibody comprises a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 56 and 72-90; and/or a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 92, 104, and 114-117. In some examples, the antibody comprises the heavy chain variable

region of antibody AL2p-h19, AL2p-h21, AL2p-h22, AL2p-h23, AL2p-h24, AL2p-h25, AL2p-h26, AL2p-h27, AL2p-h28, AL2p-h29, AL2p-h30, AL2p-h31, AL2p-h32, AL2p-h33, AL2p-h34, AL2p-h35, AL2p-h36, AL2p-h42, AL2p-h43, AL2p-h44, AL2p-h47, AL2p-h59, AL2p-h76, or AL2p-h90 (as shown in Table 6A); and/or the antibody comprises the light chain variable region of antibody AL2p-h19, AL2p-h21, AL2p-h22, AL2p-h23, AL2p-h24, AL2p-h25, AL2p-h26, AL2p-h27, AL2p-h28, AL2p-h29, AL2p-h30, AL2p-h31, AL2p-h32, AL2p-h33, AL2p-h34, AL2p-h35, AL2p-h36, AL2p-h42, AL2p-h43, AL2p-h44, AL2p-h47, AL2p-h59, AL2p-h76, or AL2p-h90 (as shown in Table 7A).

[0022] Other examples of the present disclosure relate to an antibody that binds to a TREM2 protein, wherein the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 198-213; and/or a light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 214-218. In some examples, the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 198 and 199; and a light chain comprising the amino acid sequence of SEQ ID NO: 214. In some examples, the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 200 and 201; and a light chain comprising the amino acid sequence of SEQ ID NO: 214. In some examples, the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 202 and 203; and a light chain comprising the amino acid sequence of SEQ ID NO: 215. In some examples, the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 204 and 205; and a light chain comprising the amino acid sequence of SEQ ID NO: 215. In some examples, the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 206 and 207; and a light chain comprising the amino acid sequence of SEQ ID NO: 216. In some examples, the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 208 and 209; and a light chain comprising the amino acid sequence of SEQ ID NO: 218. In some examples, the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 210 and 211; and a light chain comprising the amino acid sequence of SEQ ID NO: 218. In some examples, the antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 212 and 213; and a light chain comprising the amino acid sequence of SEQ ID NO: 217.

[0023] In some examples that may be combined with any of the preceding examples, the antibody is of the IgG class, the IgM class, or the IgA class. In some examples that may be combined with any of the preceding examples, the antibody is of the IgG class and has an IgG1, IgG2, IgG3, or IgG4 isotype. In some examples that may be combined with any of the preceding examples, the antibody comprises one or more amino acid substitutions in the Fc region at a

residue position selected from the group consisting of: C127S, L234A, L234F, L235A, L235E, S267E, K322A, L328F, A330S, P331S, E345R, E430G, S440Y, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering. In some examples that may be combined with any of the preceding examples: (a) the Fc region comprises an amino acid substitution at positions E430G, L243A, L235A, and P331S, wherein the numbering of the residue position is according to EU numbering; (b) the Fc region comprises an amino acid substitution at positions E430G and P331S, wherein the numbering of the residue position is according to EU numbering; (c) the Fc region comprises an amino acid substitution at positions E430G and K322A, wherein the numbering of the residue position is according to EU numbering; (d) the Fc region comprises an amino acid substitution at positions E430G, A330S, and P331S, wherein the numbering of the residue position is according to EU numbering; (e) the Fc region comprises an amino acid substitution at positions E430G, K322A, A330S, and P331S, wherein the numbering of the residue position is according to EU numbering; (f) the Fc region comprises an amino acid substitution at positions E430G, K322A, and A330S, wherein the numbering of the residue position is according to EU numbering; (g) the Fc region comprises an amino acid substitution at positions E430G, K322A, and P331S, wherein the numbering of the residue position is according to EU numbering; (h) the Fc region comprises an amino acid substitution at positions S267E and L328F, wherein the numbering of the residue position is according to EU numbering; (i) the Fc region comprises an amino acid substitution at position C127S, wherein the numbering of the residue position is according to EU numbering; (j) the Fc region comprises an amino acid substitution at positions E345R, E430G and S440Y, wherein the numbering of the residue position is according to EU numbering; or (k) the Fc region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 146-156. In some examples, the Fc region comprises an amino acid substitution at positions E430G and P331S, wherein the numbering of the residue position is according to EU numbering. In some examples, the Fc region comprises an amino acid substitution at positions E430G and K322A, wherein the numbering of the residue position is according to EU numbering. In some examples, the Fc region comprises an amino acid substitution at positions E430G, A330S, and P331S, wherein the numbering of the residue position is according to EU numbering. In some examples, the Fc region comprises the amino acid sequence of SEQ ID NO: 146. In some examples, the Fc region comprises the amino acid sequence of SEQ ID NO: 147. In some examples, the Fc region comprises the amino acid sequence of SEQ ID NO: 148. In some examples, the Fc region comprises the amino acid sequence of SEQ ID NO: 149. In some examples, the Fc region comprises the amino acid sequence of SEQ ID NO: 150. In some examples, the Fc region comprises the amino acid sequence of SEQ ID NO: 151. In some examples, the Fc region comprises the amino acid sequence of SEQ ID NO: 152. In some examples, the Fc region comprises the amino acid sequence of SEQ ID NO: 153. In some examples, the Fc region comprises the amino acid sequence of SEQ ID NO: 154. In some examples, the Fc region

comprises the amino acid sequence of SEQ ID NO: 155. In some examples, the Fc region comprises the amino acid sequence of SEQ ID NO: 156.

[0024] In some examples that may be combined with any of the preceding examples, the TREM2 protein is human protein. In some examples that may be combined with any of the preceding examples, the TREM2 protein is a wild-type protein. In some examples that may be combined with any of the preceding examples, the TREM2 protein is a naturally occurring variant. In some examples that may be combined with any of the preceding examples, the antibody is an antibody fragment that binds to one or more human proteins selected from the group consisting of human TREM2, a naturally occurring variant of human TREM2, and a disease variant of human TREM2, and optionally wherein the antibody fragment is cross-linked to a second antibody fragment that binds to one or more human proteins selected from the group consisting of human TREM2, a naturally occurring variant of human TREM2, and a disease variant of human TREM2. In some examples that may be combined with any of the preceding examples, the fragment is an Fab, Fab', Fab'-SH, F(ab')₂, Fv or scFv fragment. In some examples that may be combined with any of the preceding examples, the antibody is a monoclonal antibody. In some examples that may be combined with any of the preceding examples, the antibody is a humanized antibody.

[0025] In some examples that may be combined with any of the preceding examples, the antibody is a bispecific antibody recognizing a first antigen and a second antigen, wherein the first antigen is human TREM2 or a naturally occurring variant thereof, and the second antigen is: (a) an antigen facilitating transport across the blood-brain-barrier; (b) an antigen facilitating transport across the blood-brain-barrier selected from the group consisting of transferrin receptor (TR), insulin receptor (HIR), insulin-like growth factor receptor (IGFR), low-density lipoprotein receptor related proteins 1 and 2 (LPR-1 and 2), diphtheria toxin receptor, CRM197, a llama single domain antibody, TMEM 30(A), a protein transduction domain, TAT, Syn-B, penetratin, a poly-arginine peptide, an angiopeptide, and ANG1005; (c) a disease-causing agent selected from the group consisting of disease-causing peptides or proteins or, disease-causing nucleic acids, wherein the disease-causing nucleic acids are antisense GGCCCC (G2C4) repeat-expansion RNA, the disease-causing proteins are selected from the group consisting of amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides; (d) ligands and/or proteins expressed

on immune cells, wherein the ligands and/or proteins selected from the group consisting of CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA-4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG-3, and phosphatidylserine; and (e) a protein, lipid, polysaccharide, or glycolipid expressed on one or more tumor cells. In some examples that may be combined with any of the preceding examples, the antibody binds specifically to both human TREM2 and cynomolgus monkey TREM2. In some examples that may be combined with any of the preceding examples, the antibody has a dissociation constant (K_D) for human TREM2 and/or cynomolgus monkey TREM2 that is at least 1-fold lower than an anti-TREM2 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 27 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 56; or at least 1-fold lower than an anti-TREM2 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 91 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 103. In some examples that may be combined with any of the preceding examples, the antibody has a dissociation constant (K_D) for human TREM2 that ranges from about 9 μ M to about 100 pM, or less than 100 pM, wherein the K_D is determined at a temperature of approximately 25°C. In some examples that may be combined with any of the preceding examples, the antibody has a dissociation constant (K_D) for cynomolgus monkey TREM2 that ranges from about 50 nM to about 100 pM, or less than 100 pM, wherein the K_D is determined at a temperature of approximately 25°C. In some examples that may be combined with any of the preceding examples, the antibody binds to primary human immune cells with an affinity that is at least 10 times higher than that of an anti-TREM2 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 27 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 56; or at least 10 times higher than an anti-TREM2 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 91 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 103. In some examples that may be combined with any of the preceding examples, the antibody clusters and activates TREM2 signaling in an amount that is at least 1-fold greater than that of an anti-TREM2 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 27 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 56; or at least 1-fold greater than an anti-TREM2 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 91 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 103. In some examples that may be combined with any of the preceding examples, the antibody increases immune cell survival *in vitro* that to an extent that is greater than an anti-TREM2 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 27 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 56; or that is greater than an anti-TREM2 antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 91 and a light chain

variable region comprising the amino acid sequence of SEQ ID NO: 103. In some examples that may be combined with any of the preceding examples, the antibody has an *in vivo* half-life that is lower than a human control IgG1 antibody. In some examples that may be combined with any of the preceding examples, the antibody decreases plasma levels of soluble TREM2 *in vivo* by an amount that is at least 25% greater than that of a human control IgG1 antibody. In some examples that may be combined with any of the preceding examples, the antibody decreases plasma levels of soluble TREM2 *in vivo* by blocking cleavage, by inhibiting one or more metalloproteases, and/or by inducing internalization. In some examples, soluble TREM2 is decreased by about any of 10, 20, 30, 40, or 50%. In some examples that may be combined with any of the preceding examples, the antibody competes with one or more antibodies selected from the group consisting of AL2p-h50, AL2p-2, AL2p-3, AL2p-4, AL2p-5, AL2p-6, AL2p-7, AL2p-8, AL2p-9, AL2p-10, AL2p-11, AL2p-12, AL2p-13, AL2p-14, AL2p-15, AL2p-16, AL2p-17, AL2p-18, AL2p-19, AL2p-20, AL2p-21, AL2p-22, AL2p-23, AL2p-24, AL2p-25, AL2p-26, AL2p-27, AL2p-28, AL2p-29, AL2p-30, AL2p-31, AL2p-32, AL2p-33, AL2p-h77, AL2p-35, AL2p-36, AL2p-37, AL2p-38, AL2p-39, AL2p-40, AL2p-41, AL2p-42, AL2p-43, AL2p-44, AL2p-45, AL2p-46, AL2p-47, AL2p-48, AL2p-49, AL2p-50, AL2p-51, AL2p-52, AL2p-53, AL2p-54, AL2p-55, AL2p-56, AL2p-57, AL2p-58, AL2p-59, AL2p-60, AL2p-61, AL2p-62, AL2p-h19, AL2p-h21, AL2p-h22, AL2p-h23, AL2p-h24, AL2p-h25, AL2p-h26, AL2p-h27, AL2p-h28, AL2p-h29, AL2p-h30, AL2p-h31, AL2p-h32, AL2p-h33, AL2p-h34, AL2p-h35, AL2p-h36, AL2p-h42, AL2p-h43, AL2p-h44, AL2p-h47, AL2p-h59, AL2p-h76, AL2p-h90, and any combination thereof for binding to TREM2. In some examples that may be combined with any of the preceding examples, the antibody binds essentially the same TREM2 epitope as an antibody selected from the group consisting of: AL2p-h50, AL2p-2, AL2p-3, AL2p-4, AL2p-5, AL2p-6, AL2p-7, AL2p-8, AL2p-9, AL2p-10, AL2p-11, AL2p-12, AL2p-13, AL2p-14, AL2p-15, AL2p-16, AL2p-17, AL2p-18, AL2p-19, AL2p-20, AL2p-21, AL2p-22, AL2p-23, AL2p-24, AL2p-25, AL2p-26, AL2p-27, AL2p-28, AL2p-29, AL2p-30, AL2p-31, AL2p-32, AL2p-33, AL2p-h77, AL2p-35, AL2p-36, AL2p-37, AL2p-38, AL2p-39, AL2p-40, AL2p-41, AL2p-42, AL2p-43, AL2p-44, AL2p-45, AL2p-46, AL2p-47, AL2p-48, AL2p-49, AL2p-50, AL2p-51, AL2p-52, AL2p-53, AL2p-54, AL2p-55, AL2p-56, AL2p-57, AL2p-58, AL2p-59, AL2p-60, AL2p-61, AL2p-62, AL2p-h19, AL2p-h21, AL2p-h22, AL2p-h23, AL2p-h24, AL2p-h25, AL2p-h26, AL2p-h27, AL2p-h28, AL2p-h29, AL2p-h30, AL2p-h31, AL2p-h32, AL2p-h33, AL2p-h34, AL2p-h35, AL2p-h36, AL2p-h42, AL2p-h43, AL2p-h44, AL2p-h47, AL2p-h59, AL2p-h76, and AL2p-h90. In some examples that may be combined with any of the preceding examples, the antibody binds to one or more amino acids within amino acid residues 149-157 of SEQ ID NO: 1. In some examples that may be combined with any of the preceding examples, the antibody binds to one or more amino acid residues selected from the group consisting of E151, D152, and E156 of SEQ ID NO: 1.

[0026] Other examples of the present disclosure relate to an isolated nucleic acid comprising a nucleic acid sequence encoding the antibody of any one of the preceding examples. Other examples of the present disclosure relate to a vector comprising the nucleic acid of any one of the preceding examples. Other examples of the present disclosure relate to an isolated host cell comprising the vector of any one of the preceding examples. Other examples of the present disclosure relate to a method of producing an antibody that binds to TREM2, comprising culturing the cell of any one of the preceding examples so that the antibody is produced. In some examples, the method further comprises recovering the antibody produced by the cell. Other examples of the present disclosure relate to an isolated antibody that binds to TREM2 produced by the method of any one of the preceding examples. Other examples of the present disclosure relate to a pharmaceutical composition comprising the antibody of any one of the preceding examples and a pharmaceutically acceptable carrier.

[0027] Other examples of the present disclosure relate to a method of preventing, reducing risk, or treating an individual having a disease, disorder, or injury selected from the group consisting of dementia, frontotemporal dementia, Alzheimer's disease, Nasu-Hakola disease, cognitive deficit, memory loss, spinal cord injury, traumatic brain injury, multiple sclerosis, chronic colitis, ulcerative colitis, and cancer, comprising administering to an individual in need thereof a therapeutically effective amount of the antibody of the preceding examples. In some examples, the disease, disorder, or injury is Alzheimer's disease.

[0028] Other examples of the present disclosure relate to an antibody comprising an Fc region, wherein the antibody comprises an amino acid substitution at position E430G and one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: L234F, L235A, L235E, S267E, K322A, L328F, A330S, P331S, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering. In some examples: (a) the Fc region comprises an amino acid substitution at positions E430G, L243A, L235A, and P331S, wherein the numbering of the residue position is according to EU numbering; (b) the Fc region comprises an amino acid substitution at positions E430G and P331S, wherein the numbering of the residue position is according to EU numbering; (c) the Fc region comprises an amino acid substitution at positions E430G and K322A, wherein the numbering of the residue position is according to EU numbering; (d) the Fc region comprises an amino acid substitution at positions E430G, A330S, and P331S, wherein the numbering of the residue position is according to EU numbering; (e) the Fc region comprises an amino acid substitution at positions E430G, K322A, A330S, and P331S, wherein the numbering of the residue position is according to EU numbering; (f) the Fc region comprises an amino acid substitution at positions E430G, K322A, and A330S, wherein the numbering of the residue position is according to EU numbering; (g) the Fc region comprises an amino acid substitution at positions E430G, K322A, and P331S, wherein the numbering of the residue position is according to EU numbering; (h) the Fc region comprises an amino acid sequence selected from the group consisting

of SEQ ID NOs: 146-156. In some examples, the Fc region comprises an amino acid substitution at positions E430G, L243A, L235A, and P331S, wherein the numbering of the residue position is according to EU numbering. In some examples, the Fc region comprises an amino acid substitution at positions E430G and P331S, wherein the numbering of the residue position is according to EU numbering. In some examples, the Fc region comprises an amino acid substitution at positions E430G and K322A, wherein the numbering of the residue position is according to EU numbering. In some examples, the Fc region comprises an amino acid substitution at positions E430G, A330S, and P331S, wherein the numbering of the residue position is according to EU numbering. In some examples, the Fc region comprises an amino acid substitution at positions E430G, K322A, A330S, and P331S, wherein the numbering of the residue position is according to EU numbering. In some examples, the Fc region comprises an amino acid substitution at positions E430G, K322A, and A330S, wherein the numbering of the residue position is according to EU numbering. In some examples, the Fc region comprises an amino acid substitution at positions E430G, K322A, and P331S, wherein the numbering of the residue position is according to EU numbering. In some examples, the Fc region increases clustering without activating complement as compared to a corresponding antibody comprising an Fc region that does not comprise the amino acid substitutions. In some examples, the antibody induces one or more activities of a target specifically bound by the antibody. In some examples, the antibody binds to TREM2.

[0028a] In one aspect, the present disclosure refers to an antibody comprising an Fc region, wherein the antibody comprises an amino acid substitution at position E430G and one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: L234F, L235A, L235E, S267E, K322A, L328F, A330S, P331S, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering; wherein the antibody binds to TREM2; and wherein the antibody is of the IgG class and has an IgG1 isotype.

[0029] It is to be understood that one, some, or all of the properties of the various examples described herein may be combined to form other examples of the present disclosure. These and other examples of the disclosure will become apparent to one of skill in the art. These and other examples of the disclosure are further described by the detailed description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] **FIG. 1A** shows increased agonistic activity of Fc variant anti-TREM2 antibodies.

Luciferase activity after 6h culture with Fc variants of an anti-TREM2 antibody. **FIG. 1B** shows increased agonistic activity of Fc variant anti-TREM2 antibodies. Luciferase activity after 6hr co-culture of Fc variant antibodies with BWZ reporter cells and THP-1 cells in 1:1 ratio.

[0031] **FIG. 2A** shows C3b deposition induced by Fc variant anti-TREM2 antibodies. Fold change of C3b deposition on HEK expressing TREM2 cell line by AL2p Fc variants over human IgG1 isotype control antibody at 10 µg/mL. **FIG. 2B** shows C3b deposition induced by Fc variant anti-TREM2 antibodies. Fold change of C3b deposition by AL2p affinity matured variants with the listed Fc mutations over their parental IgG1 Fc variant.

[0032] **FIG. 3A** shows increased activity of soluble anti-TREM2 antibodies. **FIG. 3B** shows increased activity of plate bound anti-TREM2 antibodies. **FIG. 3C** shows reporter activity of affinity matured anti-TREM2 antibodies plate bound at 5 µg/ml (grey bars) compared to parental humanized

CLAIMS

What is claimed is:

1. An antibody comprising an Fc region, wherein the antibody comprises an amino acid substitution at position E430G and one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: L234F, L235A, L235E, S267E, K322A, L328F, A330S, P331S, and any combination thereof, wherein the numbering of the residues is according to EU or Kabat numbering; wherein the antibody binds to TREM2; and wherein the antibody is of the IgG class and has an IgG1 isotype.
2. The antibody of claim 1, wherein:
 - (a) the Fc region comprises an amino acid substitution at positions E430G, L243A, L235A, and P331S, wherein the numbering of the residue position is according to EU numbering;
 - (b) the Fc region comprises an amino acid substitution at positions E430G and P331S, wherein the numbering of the residue position is according to EU numbering;
 - (c) the Fc region comprises an amino acid substitution at positions E430G and K322A, wherein the numbering of the residue position is according to EU numbering;
 - (d) the Fc region comprises an amino acid substitution at positions E430G, A330S, and P331S, wherein the numbering of the residue position is according to EU numbering;
 - (e) the Fc region comprises an amino acid substitution at positions E430G, K322A, A330S, and P331S, wherein the numbering of the residue position is according to EU numbering;
 - (f) the Fc region comprises an amino acid substitution at positions E430G, K322A, and A330S, wherein the numbering of the residue position is according to EU numbering;
 - (g) the Fc region comprises an amino acid substitution at positions E430G, K322A, and P331S, wherein the numbering of the residue position is according to EU numbering;
 - or
 - (h) the Fc region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 146-156.
3. The antibody of claim 1 or claim 2, wherein the Fc region increases clustering without activating complement as compared to a corresponding antibody comprising an Fc region that does not comprise the amino acid substitutions.
4. The antibody of any one of claims 1 to 3, wherein the antibody induces one or more activities of TREM2.