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 OF THE PRESENT DISCLOSURE

[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 aspects 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, anti-TREM2 antibodies of the present disclosure may also have improved *in vivo* half-lives. In some embodiments, anti-TREM2 antibodies of the present disclosure may also decreases plasma levels of soluble TREM2 *in vivo*. In some embodiments, anti-TREM2 antibodies of the present disclosure may also decrease soluble TREM2. In some embodiments, the soluble TREM2 is decreased about any of 10, 20, 30, 40, 50 or 60%.

[0010] Accordingly, certain aspects of the present disclosure relate to 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: $YAFX_1X_2X_3WMN$, wherein X_1 is S or W, X_2 is S, L, or R, and X_3 is S, D, H, Q, or E (SEQ ID NO: 121); an HVR-H2 comprising the sequence according to Formula II: $RIYPGX_1GX_2TNYAX_3KX_4X_5G$, wherein X_1 is D, G, E, Q, or V, X_2 is D or Q, X_3 is Q, R, H, W, Y, or G, X_4 is F, R, or W, and X_5 is Q, R, K, or H (SEQ ID NO: 122); and an HVR-H3 comprising the sequence according to Formula III: $ARLLRNX_1PGX_2SYAX_3DY$, wherein X_1 is Q or K, X_2 is E, S, or A, and X_3 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 aspects 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: $RX_1SX_2SLX_3HSNX_4YTYLH$, wherein X_1 is S or T, X_2 is Q, R, or S, X_3 is V or I, and X_4 is G, R, W, Q, or A (SEQ ID NO: 127); an HVR-L2 comprising the sequence according to Formula V: $KVSNRX_1S$, wherein X_1 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 aspects 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: $YAFX_1X_2X_3WMN$, wherein X_1 is S or W, X_2 is S, L, or R, and X_3 is S, D, H, Q, or E (SEQ ID NO: 121); an HVR-H2 comprising the sequence according to Formula II: $RIYPGX_1GX_2TNYAX_3KX_4X_5G$, wherein X_1 is D, G, E, Q, or V, X_2 is D or Q, X_3 is Q, R, H, W, Y, or G, X_4 is F, R, or W, and X_5 is Q, R, K, or H (SEQ ID NO: 122); and an HVR-H3 comprising the

sequence according to Formula III: ARLLRNX$_1$PGX$_2$SYAX$_3$DY, wherein X$_1$ is Q or K, X$_2$ is E, S, or A, and X$_3$ 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: RX$_1$SX$_2$SLX$_3$HSNX$_4$YTYLH, wherein X$_1$ is S or T, X$_2$ is Q, R, or S, X$_3$ is V or I, and X$_4$ is G, R, W, Q, or A (SEQ ID NO: 127); an HVR-L2 comprising the sequence according to Formula V: KVSNRX$_1$S, wherein X$_1$ 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 aspects 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 aspects 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 aspects 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 aspects 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 aspects 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 aspects 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 embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments: (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 KVSNRRS (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 KVSNRFS (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 KVSNRVS (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 KVSNRRS (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 KVSNRFS (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 KVSNRFS (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 KVSNRRS (SEQ ID NO: 134), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 129). In some embodiments that may be combined with any of the

preceding embodiments, 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 KVSNRRS (SEQ ID NO: 134), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 129). In some embodiments that may be combined with any of the preceding embodiments, 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 KVSNRFS (SEQ ID NO: 131), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 129). In some embodiments that may be combined with any of the preceding embodiments, 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 KVSNRVS (SEQ ID NO: 140), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 129). In some embodiments that may be combined with any of the preceding embodiments, 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 KVSNRRS (SEQ ID NO: 134), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 129). In some embodiments that may be combined with any of the preceding embodiments, 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 KVSNRFS (SEQ ID NO: 131), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 129). In some embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, 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 KVSNRRS (SEQ ID NO: 134), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 129). In some embodiments, 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).

[0014] Other aspects 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 embodiments, 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 embodiments, 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 KVSNRFS (SEQ ID NO: 131); and a CDR-L3 comprising the sequence of SQSTRVPYT (SEQ ID NO: 129). In some embodiments, 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 KVSNRFS (SEQ ID NO: 131); and a CDR-L3 comprising the sequence of SQSTRVPYT (SEQ ID NO: 129).

[0015] Other aspects 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 embodiments, 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 embodiments, 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 embodiments, 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); 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 aspects 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 embodiments, 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 embodiments, 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 embodiments, 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 aspects 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 embodiments, 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 embodiments, 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 KVSNRRS (SEQ ID NO: 134); and a CDR-L3 comprising the sequence of SQSTRVPYT (SEQ ID NO: 129). In some embodiments, 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 KVSNRRS (SEQ ID NO: 134); and a CDR-L3 comprising the sequence of SQSTRVPYT (SEQ ID NO: 129).

[0018] Other aspects 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 embodiments, 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 embodiments, 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 KVSNRRS (SEQ ID NO: 134); and a CDR-L3 comprising the sequence of SQSTRVPYT (SEQ ID NO: 129). In some embodiments, 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 KVSNRRS (SEQ ID NO: 134); and a CDR-L3 comprising the sequence of SQSTRVPYT (SEQ ID NO: 129).

[0019] Other aspects 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 embodiments, 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 embodiments: (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 embodiments, the antibody comprises an Fc region comprising an amino acid sequence selected from the group consisting of SEQ ID Nos: 146-156. In some embodiments, the antibody comprises an Fc region comprising the amino acid sequence of SEQ ID NO: 146. In some embodiments, the antibody comprises an Fc region comprising the amino acid sequence of SEQ ID NO: 147. In some embodiments, the antibody comprises an Fc region comprising the amino acid sequence of SEQ ID NO: 148. In some embodiments, the antibody comprises an Fc region comprising the amino acid sequence of SEQ ID NO: 149. In some embodiments, the antibody comprises an Fc region comprising the amino acid sequence of SEQ ID NO: 150. In some embodiments, the antibody comprises an Fc region comprising the amino acid sequence of SEQ ID NO: 151. In some embodiments, the antibody comprises an Fc region comprising the amino acid sequence of SEQ ID NO: 152. In some embodiments, the antibody comprises an Fc region comprising the amino acid sequence of SEQ ID NO: 153. In some embodiments, the antibody comprises an Fc region comprising the amino acid sequence of SEQ ID NO: 154. In some embodiments, the antibody comprises an Fc region comprising the amino acid sequence of SEQ ID NO: 155. In some embodiments, the antibody comprises an Fc region comprising the amino acid sequence of SEQ ID NO: 156. In some embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 aspects 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 embodiments, 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 aspects 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments that may be combined with any of the preceding embodiments, the antibody is of the IgG class, the IgM class, or the IgA class. In some embodiments that may be combined with any of the preceding embodiments, the antibody is of the IgG class and has an IgG1, IgG2, IgG3, or IgG4 isotype. In some embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments: (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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the Fc region comprises the amino acid sequence of SEQ ID NO: 146. In some embodiments, the Fc region comprises the amino acid sequence of SEQ ID NO: 147. In some embodiments, the Fc region comprises the amino acid sequence of SEQ ID NO: 148. In some embodiments, the Fc region comprises the amino acid sequence of SEQ ID NO: 149. In some embodiments, the Fc region comprises the amino acid sequence of SEQ ID NO: 150. In some embodiments, the Fc region comprises the amino acid sequence of SEQ ID NO: 151. In some embodiments, the Fc region comprises the amino acid sequence of SEQ ID NO: 152. In some embodiments, the Fc region comprises the amino acid sequence of SEQ ID NO: 153. In some embodiments, the Fc region comprises the amino acid sequence of SEQ ID NO: 154. In some embodiments, the Fc region

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

[0024] In some embodiments that may be combined with any of the preceding embodiments, the TREM2 protein is human protein. In some embodiments that may be combined with any of the preceding embodiments, the TREM2 protein is a wild-type protein. In some embodiments that may be combined with any of the preceding embodiments, the TREM2 protein is a naturally occurring variant. In some embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, the fragment is an Fab, Fab', Fab'-SH, F(ab')2, Fv or scFv fragment. In some embodiments that may be combined with any of the preceding embodiments, the antibody is a monoclonal antibody. In some embodiments that may be combined with any of the preceding embodiments, the antibody is a humanized antibody.

[0025] In some embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, the antibody binds specifically to both human TREM2 and cynomolgus monkey TREM2. In some embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, the antibody has a dissociation constant (K_D) for human TREM2 that ranges from about 9 μM to about 100 pM, or less than 100 pM, wherein the K_D is determined at a temperature of approximately 25°C. In some embodiments that may be combined with any of the preceding embodiments, the antibody has a dissociation constant (K_D) for cynomolgus monkey TREM2 that ranges from about 50 nM to about100 pM, or less than 100 pM, wherein the K_D is determined at a temperature of approximately 25°C. In some embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, the antibody has an *in vivo* half-life that is lower than a human control IgG1 antibody. In some embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, 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 embodiments, soluble TREM2 is decreased by about any of 10, 20, 30, 40, or 50%. In some embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, 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 embodiments that may be combined with any of the preceding embodiments, the antibody binds to one or more amino acids within amino acid residues 149-157 of SEQ ID NO: 1. In some embodiments that may be combined with any of the preceding embodiments, 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 aspects of the present disclosure relate to an isolated nucleic acid comprising a nucleic acid sequence encoding the antibody of any one of the preceding embodiments. Other aspects of the present disclosure relate to a vector comprising the nucleic acid of any one of the preceding embodiments. Other aspects of the present disclosure relate to an isolated host cell comprising the vector of any one of the preceding embodiments. Other aspects 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 embodiments so that the antibody is produced. In some embodiments, the method further comprises recovering the antibody produced by the cell. Other aspects of the present disclosure relate to an isolated antibody that binds to TREM2 produced by the method of any one of the preceding embodiments. Other aspects of the present disclosure relate to a pharmaceutical composition comprising the antibody of any one of the preceding embodiments and a pharmaceutically acceptable carrier.

[0027] Other aspects 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 embodiments. In some embodiments, the disease, disorder, or injury is Alzheimer's disease.

[0028] Other aspects 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 embodiments: (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; of (h) the Fc region comprises an amino acid sequence selected from the group consisting

of SEQ ID NOs: 146-156. In some embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the antibody induces one or more activities of a target specifically bound by the antibody. In some embodiments, the antibody binds to TREM2.

[0029] It is to be understood that one, some, or all of the properties of the various embodiments described herein may be combined to form other embodiments of the present invention. These and other aspects of the invention will become apparent to one of skill in the art. These and other embodiments of the invention 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

antibody Alp2-h50 (h50), parental humanized antibody AL2p-77 (h77), and parental murine antibody AL2p (AL2p msIgG1 parent) clones (black bars). Clones in grey bars with black outlines represent AL2p-h50 antibody variant containing different amino acid substitutions.

[0033] **FIG. 4A** shows increased activity of soluble anti-TREM2 antibodies. **FIG. 4B** shows increased activity of plate bound anti-TREM2 antibodies.

[0034] **FIG. 5A** shows sTREM2 secreted over 48h by primary human dendritic cells from donor 534 upon incubation with anti-TREM2 or control antibodies. **FIG. 5B** shows sTREM2 secreted over 48h by primary human dendritic cells from donor 535 upon incubation with anti-TREM2 or control antibodies.

[0035] **FIG. 6A** shows that there is no change in cell numbers upon incubation of primary human dendritic cells of donor 534 with anti-TREM2 or control antibodies. **FIG.6B** shows that there is no change in cell numbers upon incubation of primary human dendritic cells of donor 535 with anti-TREM2 or control antibodies.

[0036] **FIG. 7A** shows plasma sTREM2 as % of baseline levels upon single injection of 15mg/kg TREM2 antibodies AL2p-47 huIgG1, AL2p-47 huIgG1 ASPSEG, AL2p-58 huIgG1 or control huIgG1. **FIG. 7B** shows plasma sTREM2 as % of baseline levels upon single injection of 15mg/kg TREM2 antibodies AL2p-58 huIgG1, AL2p-58 huIgG1 PSEG or control huIgG1. **FIG. 7C** shows plasma sTREM2 as % of baseline levels upon single injection of 15mg/kg TREM2 antibodies AL2p-61 huIgG1 PSEG, AL2p-47 huIgG1, AL2p-58 huIgG1 or control huIgG1. **FIG. 7D** shows plasma sTREM2 in ng/ml upon single injection of 20mg/kg TREM2 antibodies AL2p msIgG1, T21-9 msIgG1 or control msIgG1.

[0037] **FIG. 8A and FIG. 8B** depict increased viability (as increase in cellular ATP) after stimulation of primary human macrophages (**FIG. 8A**) or human primary dendritic cells (**FIG. 8B**) from one donor with plate bound TREM2 antibodies vs. control IgG for 48 hours. **FIG. 8C, FIG. 8D, FIG. 8E, and FIG. 8F** depict increased viability (as increase in cellular ATP) after stimulation of primary human dendritic cells of two donors (**FIG. 8C and FIG.8D**) or human primary macrophages of two donors (**FIG.8E and FIG.8F**) with soluble AL2p-58 huIgG1 vs. control human IgG1 for 48 hours.

[0038] **FIG. 9** shows Western blot analysis of Dap12 phosphorylation in peritoneal macrophages upon treatment of either WT or TREM2 Bac-Tg mice with AL2p-58 huIgG1, AL2p-58 huIgG1 PSEG or control huIgG1. Cell lysates were immunoprecipitated with anti-TREM2; upper set of bands show staining with a phosphotyrosine antibody and lower set show total human TREM2 levels.

DETAILED DESCRIPTION OF THE PRESENT DISCLOSURE

General techniques

[0039] The techniques and procedures described or referenced herein are generally well understood and commonly employed using conventional methodology by those skilled in the art, such

as, for example, the widely utilized methodologies described in Sambrook et al., *Molecular Cloning: A Laboratory Manual* 3d edition (2001) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; *Current Protocols in Molecular Biology* (F.M. Ausubel, et al. eds., (2003)); the series *Methods in Enzymology* (Academic Press, Inc.): *PCR 2: A Practical Approach* (M.J. MacPherson, B.D. Hames and G.R. Taylor eds. (1995)), Harlow and Lane, eds. (1988) *Antibodies, A Laboratory Manual*, and *Animal Cell Culture* (R.I. Freshney, ed. (1987)); *Oligonucleotide Synthesis* (M.J. Gait, ed., 1984); *Methods in Molecular Biology*, Humana Press; *Cell Biology: A Laboratory Notebook* (J.E. Cellis, ed., 1998) Academic Press; *Animal Cell Culture* (R.I. Freshney), ed., 1987); *Introduction to Cell and Tissue Culture* (J.P. Mather and P.E. Roberts, 1998) Plenum Press; *Cell and Tissue Culture: Laboratory Procedures* (A. Doyle, J.B. Griffiths, and D.G. Newell, eds., 1993-8) J. Wiley and Sons; *Handbook of Experimental Immunology* (D.M. Weir and C.C. Blackwell, eds.); *Gene Transfer Vectors for Mammalian Cells* (J.M. Miller and M.P. Calos, eds., 1987); *PCR: The Polymerase Chain Reaction*, (Mullis et al., eds., 1994); *Current Protocols in Immunology* (J.E. Coligan et al., eds., 1991); *Short Protocols in Molecular Biology* (Wiley and Sons, 1999); *Immunobiology* (C.A. Janeway and P. Travers, 1997); *Antibodies* (P. Finch, 1997); *Antibodies: A Practical Approach* (D. Catty., ed., IRL Press, 1988-1989); *Monoclonal Antibodies: A Practical Approach* (P. Shepherd and C. Dean, eds., Oxford University Press, 2000); *Using Antibodies: A Laboratory Manual* (E. Harlow and D. Lane (Cold Spring Harbor Laboratory Press, 1999); *The Antibodies* (M. Zanetti and J. D. Capra, eds., Harwood Academic Publishers, 1995); and *Cancer: Principles and Practice of Oncology* (V.T. DeVita et al., eds., J.B. Lippincott Company, 1993).

Definitions

[0040] As used herein, the term "*preventing*" includes providing prophylaxis with respect to occurrence or recurrence of a particular disease, disorder, or condition in an individual. An individual may be predisposed to, susceptible to a particular disease, disorder, or condition, or at risk of developing such a disease, disorder, or condition, but has not yet been diagnosed with the disease, disorder, or condition.

[0041] As used herein, an individual "*at risk*" of developing a particular disease, disorder, or condition may or may not have detectable disease or symptoms of disease, and may or may not have displayed detectable disease or symptoms of disease prior to the treatment methods described herein. "At risk" denotes that an individual has one or more risk factors, which are measurable parameters that correlate with development of a particular disease, disorder, or condition, as known in the art. An individual having one or more of these risk factors has a higher probability of developing a particular disease, disorder, or condition than an individual without one or more of these risk factors.

[0042] As used herein, the term "*treatment*" refers to clinical intervention designed to alter the natural course of the individual being treated during the course of clinical pathology. Desirable effects of treatment include decreasing the rate of progression, ameliorating or palliating the pathological

state, and remission or improved prognosis of a particular disease, disorder, or condition. An individual is successfully "treated", for example, if one or more symptoms associated with a particular disease, disorder, or condition are mitigated or eliminated.

[0043] An "*effective amount*" refers to at least an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic or prophylactic result. An effective amount can be provided in one or more administrations. An effective amount herein may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the treatment to elicit a desired response in the individual. An effective amount is also one in which any toxic or detrimental effects of the treatment are outweighed by the therapeutically beneficial effects. For prophylactic use, beneficial or desired results include results such as eliminating or reducing the risk, lessening the severity, or delaying the onset of the disease, including biochemical, histological and/or behavioral symptoms of the disease, its complications and intermediate pathological phenotypes presenting during development of the disease. For therapeutic use, beneficial or desired results include clinical results such as decreasing one or more symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, enhancing effect of another medication such as via targeting, delaying the progression of the disease, and/or prolonging survival. An effective amount of drug, compound, or pharmaceutical composition is an amount sufficient to accomplish prophylactic or therapeutic treatment either directly or indirectly. As is understood in the clinical context, an effective amount of a drug, compound, or pharmaceutical composition may or may not be achieved in conjunction with another drug, compound, or pharmaceutical composition. Thus, an "effective amount" may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable result may be or is achieved.

[0044] An "*individual*" for purposes of treatment, prevention, or reduction of risk refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sport, or pet animals, such as dogs, horses, rabbits, cattle, pigs, hamsters, gerbils, mice, ferrets, rats, cats, and the like. In some embodiments, the individual is human.

[0045] As used herein, administration "*in conjunction*" with another compound or composition includes simultaneous administration and/or administration at different times. Administration in conjunction also encompasses administration as a co-formulation or administration as separate compositions, including at different dosing frequencies or intervals, and using the same route of administration or different routes of administration.

[0046] The term "*immunoglobulin*" (Ig) is used interchangeably with "*antibody*" herein. The term "antibody" herein is used in the broadest sense and specifically covers monoclonal antibodies, polyclonal antibodies, multispecific antibodies (*e.g.*, bispecific antibodies) formed from at least two intact antibodies, and antibody fragments so long as they exhibit the desired biological activity.

[0047] The basic 4-chain antibody unit is a heterotetrameric glycoprotein composed of two identical light (L) chains and two identical heavy (H) chains. The pairing of a V_H and V_L together forms a single antigen-binding site. For the structure and properties of the different classes of antibodies, *see, e.g.*, *Basic and Clinical Immunology*, 8th Ed., Daniel P. Stites, Abba I. Terr and Tristram G. Parslow (eds.), Appleton & Lange, Norwalk, CT, 1994, page 71 and Chapter 6.

[0048] The L chain from any vertebrate species can be assigned to one of two clearly distinct types, called kappa ("κ") and lambda ("λ"), based on the amino acid sequences of their constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains (CH), immunoglobulins can be assigned to different classes or isotypes. There are five classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, having heavy chains designated alpha ("α"), delta ("δ"), epsilon ("ε"), gamma ("γ") and mu ("μ"), respectively. The γ and α classes are further divided into subclasses (isotypes) on the basis of relatively minor differences in the CH sequence and function, *e.g.*, humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2. The subunit structures and three dimensional configurations of different classes of immunoglobulins are well known and described generally in, for example, Abbas *et al.*, Cellular and Molecular Immunology, 4th ed. (W.B. Saunders Co., 2000).

[0049] "*Native antibodies*" are usually heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intra-chain disulfide bridges. Each heavy chain has at one end a variable domain (V_H) followed by a number of constant domains. Each light chain has a variable domain at one end (V_L) and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains.

[0050] An "*isolated*" antibody, such as an isolated anti-TREM2 antibody of the present disclosure, is one that has been identified, separated and/or recovered from a component of its production environment (*e.g.*, naturally or recombinantly). Preferably, the isolated polypeptide is free of association with all other contaminant components from its production environment. Contaminant components from its production environment, such as those resulting from recombinant transfected cells, are materials that would typically interfere with research, diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified: (1) to greater than 95% by weight of antibody as determined by, for example, the Lowry method, and in some embodiments, to greater than 99% by weight; (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under non-

reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody *in situ* within recombinant T-cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, an isolated polypeptide or antibody will be prepared by at least one purification step.

[0051] The "*variable region*" or "*variable domain*" of an antibody, such as an anti-TREM2 antibody of the present disclosure, refers to the amino-terminal domains of the heavy or light chain of the antibody. The variable domains of the heavy chain and light chain may be referred to as "V_H" and "V_L", respectively. These domains are generally the most variable parts of the antibody (relative to other antibodies of the same class) and contain the antigen binding sites.

[0052] The term "*variable*" refers to the fact that certain segments of the variable domains differ extensively in sequence among antibodies, such as anti-TREM2 antibodies of the present disclosure. The V domain mediates antigen binding and defines the specificity of a particular antibody for its particular antigen. However, the variability is not evenly distributed across the entire span of the variable domains. Instead, it is concentrated in three segments called hypervariable regions (HVRs) both in the light-chain and the heavy chain variable domains. The more highly conserved portions of variable domains are called the framework regions (FR). The variable domains of native heavy and light chains each comprise four FR regions, largely adopting a beta-sheet configuration, connected by three HVRs, which form loops connecting, and in some cases forming part of, the beta-sheet structure. The HVRs in each chain are held together in close proximity by the FR regions and, with the HVRs from the other chain, contribute to the formation of the antigen-binding site of antibodies (*see* Kabat et al., *Sequences of Immunological Interest*, Fifth Edition, National Institute of Health, Bethesda, MD (1991)). The constant domains are not involved directly in the binding of antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody-dependent-cellular toxicity.

[0053] The term "*monoclonal antibody*" as used herein refers to an antibody, such as a monoclonal anti-TREM2 antibody of the present disclosure, obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations and/or post-translation modifications (*e.g.*, isomerizations, amidations, *etc.*) that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. In contrast to polyclonal antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention

may be made by a variety of techniques, including, for example, the hybridoma method (*e.g.*, Kohler and Milstein., *Nature*, 256:495-97 (1975); Hongo et al., *Hybridoma,* 14 (3):253-260 (1995), Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2d ed. 1988); Hammerling et al., in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681 (Elsevier, N.Y., 1981)), recombinant DNA methods (see, *e.g.*, U.S. Patent No. 4,816,567), phage-display technologies (*see, e.g.*, Clackson *et al.*, *Nature*, 352:624-628 (1991); Marks *et al.*, *J. Mol. Biol.* 222:581-597 (1992); Sidhu *et al.*, *J. Mol. Biol.* 338(2): 299-310 (2004); Lee et al., *J. Mol. Biol.* 340(5):1073-1093 (2004); Fellouse, *Proc. Nat'l Acad. Sci. USA* 101(34):12467-472 (2004); and Lee *et al.*, *J. Immunol. Methods* 284(1-2):119-132 (2004), yeast presentation technologies (see, *e.g.*, WO2009/036379A2; WO2010105256; WO2012009568, and Xu et al., *Protein Eng. Des. Sel.*, 26(10): 663-70 (2013), and technologies for producing human or human-like antibodies in animals that have parts or all of the human immunoglobulin loci or genes encoding human immunoglobulin sequences (see, *e.g.*, WO 1998/24893; WO 1996/34096; WO 1996/33735; WO 1991/10741; Jakobovits et al., *Proc. Nat'l Acad. Sci. USA* 90:2551 (1993); Jakobovits *et al.*, *Nature* 362:255-258 (1993); Bruggemann *et al.*, *Year in Immunol.* 7:33 (1993); U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and 5,661,016; Marks *et al.*, *Bio/Technology* 10:779-783 (1992); Lonberg *et al.*, *Nature* 368:856-859 (1994); Morrison, *Nature* 368:812-813 (1994); Fishwild et al., *Nature Biotechnol.* 14:845-851 (1996); Neuberger, *Nature Biotechnol.* 14:826 (1996); and Lonberg and Huszar, *Intern. Rev. Immunol.* 13:65-93 (1995).

[0054] The terms "*full-length antibody*," "*intact antibody*" or "*whole antibody*" are used interchangeably to refer to an antibody, such as an anti-TREM2 antibody of the present disclosure, in its substantially intact form, as opposed to an antibody fragment. Specifically whole antibodies include those with heavy and light chains including an Fc region. The constant domains may be native sequence constant domains (*e.g.*, human native sequence constant domains) or amino acid sequence variants thereof. In some cases, the intact antibody may have one or more effector functions.

[0055] An "*antibody fragment*" comprises a portion of an intact antibody, preferably the antigen binding and/or the variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', $F(ab')_2$ and Fv fragments; diabodies; linear antibodies (*see* U.S. Patent 5,641,870, Example 2; Zapata et al., *Protein Eng.* 8(10):1057-1062 (1995)); single-chain antibody molecules and multispecific antibodies formed from antibody fragments.

[0056] Papain digestion of antibodies, such as anti-TREM2 antibodies of the present disclosure, produces two identical antigen-binding fragments, called "*Fab*" fragments, and a residual "*Fc*" fragment, a designation reflecting the ability to crystallize readily. The Fab fragment consists of an entire L chain along with the variable region domain of the H chain (V_H), and the first constant domain of one heavy chain (C_H1). Each Fab fragment is monovalent with respect to antigen binding, *i.e.*, it has a single antigen-binding site. Pepsin treatment of an antibody yields a single large $F(ab')_2$ fragment which roughly corresponds to two disulfide linked Fab fragments having different antigen-

binding activity and is still capable of cross-linking antigen. Fab' fragments differ from Fab fragments by having a few additional residues at the carboxy terminus of the C_H1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

[0057] The Fc fragment comprises the carboxy-terminal portions of both H chains held together by disulfides. The effector functions of antibodies are determined by sequences in the Fc region, the region which is also recognized by Fc receptors (FcR) found on certain types of cells.

[0058] "*Fv*" is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This fragment consists of a dimer of one heavy- and one light-chain variable region domain in tight, non-covalent association. From the folding of these two domains emanate six hypervariable loops (3 loops each from the H and L chain) that contribute the amino acid residues for antigen binding and confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three HVRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

[0059] *"Single-chain Fv"* also abbreviated as "*sFv*" or "*scFv*" are antibody fragments that comprise the VH and VL antibody domains connected into a single polypeptide chain. Preferably, the sFv polypeptide further comprises a polypeptide linker between the V_H and V_L domains, which enables the sFv to form the desired structure for antigen binding. For a review of the sFv, *see* Plückthun in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenburg and Moore eds., Springer-VerLAG-3, New York, pp. 269-315 (1994).

[0060] "*Functional fragments*" of antibodies, such as anti-TREM2 antibodies of the present disclosure, comprise a portion of an intact antibody, generally including the antigen binding or variable region of the intact antibody or the F region of an antibody which retains or has modified FcR binding capability. Examples of antibody fragments include linear antibody, single-chain antibody molecules and multispecific antibodies formed from antibody fragments.

[0061] The term "*diabodies*" refers to small antibody fragments prepared by constructing sFv fragments (see preceding paragraph) with short linkers (about 5-10) residues) between the V_H and V_L domains such that inter-chain but not intra-chain pairing of the V domains is achieved, thereby resulting in a bivalent fragment, *i.e.*, a fragment having two antigen-binding sites. Bispecific diabodies are heterodimers of two "crossover" sFv fragments in which the V_H and V_L domains of the two antibodies are present on different polypeptide chains. Diabodies are described in greater detail in, for example, EP 404,097; WO 93/11161; Hollinger et al., *Proc. Nat'l Acad. Sci. USA* 90:6444-48 (1993).

[0062] As used herein, a "*chimeric antibody*" refers to an antibody (immunoglobulin), such as a chimeric anti-TREM2 antibody of the present disclosure, in which a portion of the heavy and/or light

chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is(are) identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Patent No. 4,816,567; Morrison et al., *Proc. Nat'l Acad. Sci. USA*, 81:6851-55 (1984)). Chimeric antibodies of interest herein include PRIMATIZED® antibodies wherein the antigen-binding region of the antibody is derived from an antibody produced by, *e.g.*, immunizing macaque monkeys with an antigen of interest. As used herein, "humanized antibody" is used a subset of "chimeric antibodies."

[0063] "*Humanized*" forms of non-human (*e.g.*, murine) antibodies, such as humanized forms of anti-TREM2 antibodies of the present disclosure, are chimeric antibodies that contain minimal sequence derived from non-human immunoglobulin. In one embodiment, a humanized antibody is a human immunoglobulin (recipient antibody) in which residues from an HVR of the recipient are replaced by residues from an HVR of a non-human species (donor antibody) such as mouse, rat, rabbit or non-human primate having the desired specificity, affinity, and/or capacity. In some instances, FR residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications may be made to further refine antibody performance, such as binding affinity. In general, a humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin sequence, and all or substantially all of the FR regions are those of a human immunoglobulin sequence, although the FR regions may include one or more individual FR residue substitutions that improve antibody performance, such as binding affinity, isomerization, immunogenicity, and the like. The number of these amino acid substitutions in the FR is typically no more than 6 in the H chain, and in the L chain, no more than 3. The humanized antibody optionally will also comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, *see, e.g.*, Jones et al., *Nature* 321:522-525 (1986); Riechmann et al., *Nature* 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.* 2:593-596 (1992). *See also*, for example, Vaswani and Hamilton, *Ann. Allergy, Asthma & Immunol.* 1:105-115 (1998); Harris, *Biochem. Soc. Transactions* 23:1035-1038 (1995); Hurle and Gross, *Curr. Op. Biotech.* 5:428-433 (1994); and U.S. Patent Nos. 6,982,321 and 7,087,409.

[0064] A "*human antibody*" is one that possesses an amino-acid sequence corresponding to that of an antibody, such as an anti-TREM2 antibody of the present disclosure, produced by a human and/or has been made using any of the techniques for making human antibodies as disclosed herein. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen-binding residues. Human antibodies can be produced using various techniques known

in the art, including phage-display libraries. Hoogenboom and Winter, *J. Mol. Biol.*, 227:381 (1991); Marks et al., *J. Mol. Biol.*, 222:581 (1991). Also available for the preparation of human monoclonal antibodies are methods described in Cole et al., *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, p. 77 (1985); Boerner et al., *J. Immunol.*, 147(1):86-95 (1991). *See also* van Dijk and van de Winkel, *Curr. Opin. Pharmacol.* 5:368-74 (2001). Human antibodies can be prepared by administering the antigen to a transgenic animal that has been modified to produce such antibodies in response to antigenic challenge, but whose endogenous loci have been disabled, *e.g.*, immunized xenomice (*see. e.g.*, U.S. Patent Nos. 6,075,181 and 6,150,584 regarding XENOMOUSE™ technology). *See also*, for example, Li et al., *Proc. Nat'l Acad. Sci. USA*, 103:3557-3562 (2006) regarding human antibodies generated via a human B-cell hybridoma technology. Alternatively, human antibodies can also be prepared by employing yeast libraries and methods as disclosed in, for example, WO2009/036379A2; WO2010105256; WO2012009568; and Xu et al., *Protein Eng. Des. Sel.*, 26(10): 663-70 (2013).

[0065] The term "*hypervariable region*," "*HVR*," or "*HV*," when used herein refers to the regions of an antibody-variable domain, such as that of an anti-TREM2 antibody of the present disclosure, that are hypervariable in sequence and/or form structurally defined loops. Generally, antibodies comprise six HVRs; three in the VH (H1, H2, H3), and three in the VL (L1, L2, L3). In native antibodies, H3 and L3 display the most diversity of the six HVRs, and H3 in particular is believed to play a unique role in conferring fine specificity to antibodies. *See, e.g.*, Xu et al., *Immunity* 13:37-45 (2000); Johnson and Wu in *Methods in Molecular Biology* 248:1-25 (Lo, ed., Human Press, Totowa, NJ, 2003)). Indeed, naturally occurring camelid antibodies consisting of a heavy chain only are functional and stable in the absence of light chain. See, *e.g.*, Hamers-Casterman et al., *Nature* 363:446-448 (1993) and Sheriff et al., *Nature Struct. Biol.* 3:733-736 (1996).

[0066] A number of HVR delineations are in use and are encompassed herein. In some embodiments, the HVRs may be Kabat complementarity-determining regions (CDRs) based on sequence variability and are the most commonly used (Kabat et al., *supra*). In some embodiments, the HVRs may be Chothia CDRs. Chothia refers instead to the location of the structural loops (Chothia and Lesk *J. Mol. Biol.* 196:901-917 (1987)). In some embodiments, the HVRs may be AbM HVRs. The AbM HVRs represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular's AbM antibody-modeling software. In some embodiments, the HVRs may be "contact" HVRs. The "contact" HVRs are based on an analysis of the available complex crystal structures. The residues from each of these HVRs are noted below.

Loop	Kabat	AbM	Chothia	Contact	
L1	L24-L34	L24-L34	L26-L32	L30-L36	
L2	L50-L56	L50-L56	L50-L52	L46-L55	
L3	L89-L97	L89-L97	L91-L96	L89-L96	
H1	H31-H35B	H26-H35B	H26-H32	H30-H35B (Kabat numbering)	
H1	H31-H35	H26-H35	H26-H32	H30-H35 (Chothia numbering)	
H2	H50-H65	H50-H58	H53-H55	H47-H58	

H3	H95-H102	H95-H102	H96-H101	H93-H101

[0067] HVRs may comprise "extended HVRs" as follows: 24-36 or 24-34 (L1), 46-56 or 50-56 (L2), and 89-97 or 89-96 (L3) in the VL, and 26-35 (H1), 50-65 or 49-65 (a preferred embodiment) (H2), and 93-102, 94-102, or 95-102 (H3) in the VH. The variable-domain residues are numbered according to Kabat et al., *supra*, for each of these extended-HVR definitions.

[0068] "*Framework*" or "*FR*" residues are those variable-domain residues other than the HVR residues as herein defined.

[0069] The phrase "*variable-domain residue-numbering as in Kabat*" or "*amino-acid-position numbering as in Kabat*," and variations thereof, refers to the numbering system used for heavy-chain variable domains or light-chain variable domains of the compilation of antibodies in Kabat et al., *supra*. Using this numbering system, the actual linear amino acid sequence may contain fewer or additional amino acids corresponding to a shortening of, or insertion into, a FR or HVR of the variable domain. For example, a heavy-chain variable domain may include a single amino acid insert (residue 52a according to Kabat) after residue 52 of H2 and inserted residues (*e.g.*, residues 82a, 82b, and 82c, *etc.* according to Kabat) after heavy-chain FR residue 82. The Kabat numbering of residues may be determined for a given antibody by alignment at regions of homology of the sequence of the antibody with a "standard" Kabat numbered sequence.

[0070] The Kabat numbering system is generally used when referring to a residue in the variable domain (approximately residues 1-107 of the light chain and residues 1-113 of the heavy chain) (*e.g.*, Kabat et al., Sequences of Immunological Interest. 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)). The "EU or, Kabat numbering system" or "EU index" is generally used when referring to a residue in an immunoglobulin heavy chain constant region (*e.g.*, the EU index reported in Kabat *et al., supra*). The "EU index as in Kabat" refers to the residue numbering of the human IgG1 EU antibody. References to residue numbers in the variable domain of antibodies means residue numbering by the Kabat numbering system. References to residue numbers in the constant domain of antibodies means residue numbering by the EU or, Kabat numbering system (*e.g.*, *see* United States Patent Publication No. 2010-280227).

[0071] An "*acceptor human framework*" as used herein is a framework comprising the amino acid sequence of a VL or VH framework derived from a human immunoglobulin framework or a human consensus framework. An acceptor human framework "derived from" a human immunoglobulin framework or a human consensus framework may comprise the same amino acid sequence thereof, or it may contain pre-existing amino acid sequence changes. In some embodiments, the number of pre-existing amino acid changes are 10 or less, 9 or less, 8 or less, 7 or less, 6 or less, 5 or less, 4 or less, 3 or less, or 2 or less. Where pre-existing amino acid changes are present in a VH, preferable those changes occur at only three, two, or one of positions 71H, 73H and 78H; for instance, the amino acid residues at those positions may by 71A, 73T and/or 78A. In one embodiment, the VL

acceptor human framework is identical in sequence to the VL human immunoglobulin framework sequence or human consensus framework sequence.

[0072] A "*human consensus framework*" is a framework that represents the most commonly occurring amino acid residues in a selection of human immunoglobulin VL or VH framework sequences. Generally, the selection of human immunoglobulin VL or VH sequences is from a subgroup of variable domain sequences. Generally, the subgroup of sequences is a subgroup as in Kabat et al., *Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (1991). Examples include for the VL, the subgroup may be subgroup kappa I, kappa II, kappa III or kappa IV as in Kabat *et al., supra.* Additionally, for the VH, the subgroup may be subgroup I, subgroup II, or subgroup III as in Kabat *et al., supra.*

[0073] An "*amino-acid modification*" at a specified position, *e.g.*, of an anti-TREM2 antibody of the present disclosure, refers to the substitution or deletion of the specified residue, or the insertion of at least one amino acid residue adjacent the specified residue. Insertion "adjacent" to a specified residue means insertion within one to two residues thereof. The insertion may be N-terminal or C-terminal to the specified residue. The preferred amino acid modification herein is a substitution.

[0074] An "*affinity-matured*" antibody, such as an affinity matured anti-TREM2 antibody of the present disclosure, is one with one or more alterations in one or more HVRs thereof that result in an improvement in the affinity of the antibody for antigen, compared to a parent antibody that does not possess those alteration(s). In one embodiment, an affinity-matured antibody has nanomolar or even picomolar affinities for the target antigen. Affinity-matured antibodies are produced by procedures known in the art. For example, Marks et al., *Bio/Technology* 10:779-783 (1992) describes affinity maturation by VH- and VL-domain shuffling. Random mutagenesis of HVR and/or framework residues is described by, for example: Barbas et al. *Proc Nat. Acad. Sci. USA* 91:3809-3813 (1994); Schier et al. *Gene* 169:147-155 (1995); Yelton et al. *J. Immunol.* 155:1994-2004 (1995); Jackson et al., *J. Immunol.* 154(7):3310-9 (1995); and Hawkins *et al, J. Mol. Biol.* 226:889-896 (1992).

[0075] As use herein, the term "*specifically recognizes*" or "*specifically binds*" refers to measurable and reproducible interactions such as attraction or binding between a target and an antibody, such as between an anti-TREM2 antibody and TREM2 that is determinative of the presence of the target in the presence of a heterogeneous population of molecules including biological molecules. For example, an antibody, such as an anti-TREM2 antibody of the present disclosure, that specifically or preferentially binds to a target or an epitope is an antibody that binds this target or epitope with greater affinity, avidity, more readily, and/or with greater duration than it binds to other targets or other epitopes of the target. It is also understood by reading this definition that, for example, an antibody (or a moiety) that specifically or preferentially binds to a first target may or may not specifically or preferentially bind to a second target. As such, "*specific binding*" or "*preferential binding*" does not necessarily require (although it can include) exclusive binding. An antibody that specifically binds to a target may have an association constant of at least about $10^{3}\ M^{-1}$ or $10^{4}\ M^{-1}$,

sometimes about $10^{5}\ M^{-1}$ or $10^{6}\ M^{-1}$, in other instances about $10^{6}\ M^{-1}$ or $10^{7}\ M^{-1}$, about $10^{8}\ M^{-1}$ to $10^{9}\ M^{-1}$, or about $10^{10}\ M^{-1}$ to $10^{11}\ M^{-1}$ or higher. A variety of immunoassay formats can be used to select antibodies specifically immunoreactive with a particular protein. For example, solid-phase ELISA immunoassays are routinely used to select monoclonal antibodies specifically immunoreactive with a protein. *See, e.g.*, Harlow and Lane (1988) Antibodies, A Laboratory Manual, Cold Spring Harbor Publications, New York, for a description of immunoassay formats and conditions that can be used to determine specific immunoreactivity.

[0076] As used herein, an "*interaction*" between a TREM2 protein and a second protein encompasses, without limitation, protein-protein interaction, a physical interaction, a chemical interaction, binding, covalent binding, and ionic binding. As used herein, an antibody "inhibits interaction" between two proteins when the antibody disrupts, reduces, or completely eliminates an interaction between the two proteins. An antibody of the present disclosure, or fragment thereof, "inhibits interaction" between two proteins when the antibody or fragment thereof binds to one of the two proteins.

[0077] An "*agonist*" antibody or an "*activating*" antibody is an antibody that induces (*e.g.*, increases) one or more activities or functions of the antigen after the antibody binds the antigen.

[0078] An "*antagonist*" antibody or a "*blocking*" antibody is an antibody that reduces or eliminates (*e.g.*, decreases) antigen binding to one or more ligand after the antibody binds the antigen, and/or that reduces or eliminates (*e.g.*, decreases) one or more activities or functions of the antigen after the antibody binds the antigen. In some embodiments, antagonist antibodies, or blocking antibodies substantially or completely inhibit antigen binding to one or more ligand and/or one or more activities or functions of the antigen.

[0079] Antibody "*effector functions*" refer to those biological activities attributable to the Fc region (a native sequence Fc region or amino acid sequence variant Fc region) of an antibody, and vary with the antibody isotype.

[0080] The term "*Fc region*" herein is used to define a C-terminal region of an immunoglobulin heavy chain, including native-sequence Fc regions and variant Fc regions. Although the boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy-chain Fc region is usually defined to stretch from an amino acid residue at position Cys226, or from Pro230, to the carboxyl-terminus thereof. The C-terminal lysine (residue 447 according to the EU or, Kabat numbering system) of the Fc region may be removed, for example, during production or purification of the antibody, or by recombinantly engineering the nucleic acid encoding a heavy chain of the antibody. Accordingly, a composition of intact antibodies may comprise antibody populations with all K447 residues removed, antibody populations with no K447 residues removed, and antibody populations having a mixture of antibodies with and without the K447 residue. Suitable native-sequence Fc regions for use in the antibodies of the present disclosure include human IgG1, IgG2, IgG3 and IgG4.

[0081] A "*native sequence Fc region*" comprises an amino acid sequence identical to the amino acid sequence of an Fc region found in nature. Native sequence human Fc regions include a native sequence human IgG1 Fc region (non-A and A allotypes); native sequence human IgG2 Fc region; native sequence human IgG3 Fc region; and native sequence human IgG4 Fc region as well as naturally occurring variants thereof.

[0082] A "*variant Fc region*" comprises an amino acid sequence which differs from that of a native sequence Fc region by virtue of at least one amino acid modification, preferably one or more amino acid substitution(s). Preferably, the variant Fc region has at least one amino acid substitution compared to a native sequence Fc region or to the Fc region of a parent polypeptide, *e.g.* from about one to about ten amino acid substitutions, and preferably from about one to about five amino acid substitutions in a native sequence Fc region or in the Fc region of the parent polypeptide. The variant Fc region herein will preferably possess at least about 80% homology with a native sequence Fc region and/or with an Fc region of a parent polypeptide, and most preferably at least about 90% homology therewith, more preferably at least about 95% homology therewith.

[0083] "*Fc receptor*" or "*FcR*" describes a receptor that binds to the Fc region of an antibody. The preferred FcR is a native sequence human FcR. Moreover, a preferred FcR is one which binds an IgG antibody (a gamma receptor) and includes receptors of the FcγRI, FcγRII, and FcγRIII subclasses, including allelic variants and alternatively spliced forms of these receptors, FcγRII receptors include FcγRIIA (an "activating receptor") and FcγRIIB (an "inhibiting receptor"), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. Activating receptor FcγRIIA contains an immunoreceptor tyrosine-based activation motif ("ITAM") in its cytoplasmic domain. Inhibiting receptor FcγRIIB contains an immunoreceptor tyrosine-based inhibition motif ("ITIM") in its cytoplasmic domain. (*see, e.g.*, M. Daëron, *Annu. Rev. Immunol.* 15:203-234 (1997)). FcRs are reviewed in Ravetch and Kinet, *Annu. Rev. Immunol.* 9:457-92 (1991); Capel et al., *Immunomethods* 4:25-34 (1994); and de Haas et al., *J. Lab. Clin. Med.* 126: 330-41 (1995). Other FcRs, including those to be identified in the future, are encompassed by the term "FcR" herein. FcRs can also increase the serum half-life of antibodies.

[0084] Binding to FcRn *in vivo* and serum half-life of human FcRn high-affinity binding polypeptides can be assayed, *e.g.*, in transgenic mice or transfected human cell lines expressing human FcRn, or in primates to which the polypeptides having a variant Fc region are administered. WO 2004/42072 (Presta) describes antibody variants with improved or diminished binding to FcRs. *See also, e.g.*, Shields et al., *J. Biol. Chem.* 9(2):6591-6604 (2001).

[0085] As used herein, "*percent (%) amino acid sequence identity*" and "*homology*" with respect to a peptide, polypeptide or antibody sequence refers to the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific peptide or polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the

sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or MEGALIGN™ (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms known in the art needed to achieve maximal alignment over the full-length of the sequences being compared.

[0086] An "*isolated*" nucleic acid molecule encoding an antibody, such as an anti-TREM2 antibody of the present disclosure, is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the environment in which it was produced. Preferably, the isolated nucleic acid is free of association with all components associated with the production environment. The isolated nucleic acid molecules encoding the polypeptides and antibodies herein is in a form other than in the form or setting in which it is found in nature. Isolated nucleic acid molecules therefore are distinguished from nucleic acid encoding the polypeptides and antibodies herein existing naturally in cells.

[0087] The term "*vector*," as used herein, is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid," which refers to a circular double stranded DNA into which additional DNA segments may be ligated. Another type of vector is a phage vector. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "recombinant expression vectors," or simply, "expression vectors." In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" may be used interchangeably as the plasmid is the most commonly used form of vector.

[0088] "*Polynucleotide*," or "*nucleic acid*," as used interchangeably herein, refer to polymers of nucleotides of any length, and include DNA and RNA. The nucleotides can be deoxyribonucleotides, ribonucleotides, modified nucleotides or bases, and/or their analogs, or any substrate that can be incorporated into a polymer by DNA or RNA polymerase or by a synthetic reaction. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and their analogs. If present, modification to the nucleotide structure may be imparted before or after assembly of the polymer. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may comprise modification(s) made after synthesis, such as conjugation to a label. Other types of modifications include, for example, "caps," substitution of one or more of the naturally occurring

nucleotides with an analog, internucleotide modifications such as, for example, those with uncharged linkages (*e.g.*, methyl phosphonates, phosphotriesters, phosphoamidates, carbamates, *etc.*) and with charged linkages (*e.g.*, phosphorothioates, phosphorodithioates, *etc.*), those containing pendant moieties, such as, for example, proteins (*e.g.*, nucleases, toxins, antibodies, signal peptides, ply-L-lysine, *etc.*), those with intercalators (*e.g.*, acridine, psoralen, *etc.*), those containing chelators (*e.g.*, metals, radioactive metals, boron, oxidative metals, *etc.*), those containing alkylators, those with modified linkages (*e.g.*, alpha anomeric nucleic acids, *etc.*), as well as unmodified forms of the polynucleotides(s). Further, any of the hydroxyl groups ordinarily present in the sugars may be replaced, for example, by phosphonate groups, phosphate groups, protected by standard protecting groups, or activated to prepare additional linkages to additional nucleotides, or may be conjugated to solid or semi-solid supports. The 5' and 3' terminal OH can be phosphorylated or substituted with amines or organic capping group moieties of from 1 to 20 carbon atoms. Other hydroxyls may also be derivatized to standard protecting groups. Polynucleotides can also contain analogous forms of ribose or deoxyribose sugars that are generally known in the art, including, for example, 2'-O-methyl-, 2'-O-allyl-, 2'-fluoro- or 2'-azido-ribose, carbocyclic sugar analogs, α-anomeric sugars, epimeric sugars such as arabinose, xyloses or lyxoses, pyranose sugars, furanose sugars, sedoheptuloses, acyclic analogs, and basic nucleoside analogs such as methyl riboside. One or more phosphodiester linkages may be replaced by alternative linking groups. These alternative linking groups include, but are not limited to, embodiments wherein phosphate is replaced by P(O)S ("thioate"), P(S)S ("dithioate"), (O)NR2 ("amidate"), P(O)R, P(O)OR', CO, or CH2 ("formacetal"), in which each R or R' is independently H or substituted or unsubstituted alkyl (1-20 C) optionally containing an ether (-O-) linkage, aryl, alkenyl, cycloalkyl, cycloalkenyl or araldyl. Not all linkages in a polynucleotide need be identical. The preceding description applies to all polynucleotides referred to herein, including RNA and DNA.

[0089] A "*host cell*" includes an individual cell or cell culture that can be or has been a recipient for vector(s) for incorporation of polynucleotide inserts. Host cells include progeny of a single host cell, and the progeny may not necessarily be completely identical (in morphology or in genomic DNA complement) to the original parent cell due to natural, accidental, or deliberate mutation. A host cell includes cells transfected *in vivo* with a polynucleotide(s) of this invention.

[0090] "*Carriers*" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers that are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or

dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN™, polyethylene glycol (PEG), and PLURONICS™.

[0091] The term "*about*" as used herein refers to the usual error range for the respective value readily known to the skilled person in this technical field. Reference to "*about*" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter *per se*.

[0092] As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly indicates otherwise. For example, reference to an "antibody" is a reference to from one to many antibodies, such as molar amounts, and includes equivalents thereof known to those skilled in the art, and so forth.

[0093] It is understood that aspect and embodiments of the present disclosure described herein include "comprising," "consisting," and "consisting essentially of" aspects and embodiments.

Overview

[0094] The present disclosure relates to anti-TREM2 antibodies (*e.g.*, monoclonal antibodies) with improved affinity and functional characteristics; methods of making and using such antibodies; pharmaceutical compositions containing such antibodies; nucleic acids encoding such antibodies; and host cells containing nucleic acids encoding such antibodies.

[0095] Accordingly, certain aspects of the present disclosure are based, at least in part, on the identification of anti-TREM2 antibodies that are capable of binding to both human and cynomolgus monkey TREM2 with high affinity (*see, e.g.*, **Examples 2 and 6**); that are capable of binding to primary human immune cells with high affinity (*see, e.g.*, **Examples 1-3**); that have improved capability of clustering and activating TREM2 signaling *in vitro* and *in vivo* (*see, e.g.*, **Examples 3, 7, and 11**); and that have improved capability of increase immune cell survival *in vitro* (*see, e.g.*, **Examples 3 and 9**). Advantageously, anti-TREM2 antibodies of the present disclosure were shown have improved *in vivo* half-lives and to be able decreases plasma levels of soluble TREM2 *in vitro* and *in vivo* (*see, e.g.*, **Examples 4, 8, and 10**). In some embodiments, anti-TREM2 antibodies of the present disclosure induce, increase, or otherwise enhance one or more TREM2 activities of the present disclosure. In some embodiments, anti-TREM2 antibodies of the present disclosure have one or more of these improved affinity and functional characteristics, as compared to an anti-TREM2 antibody having the heavy chain variable region and light chain variable region of antibody AL2p-h50 or AL2p-h77. Moreover, based on the results described in **Examples 2-11**, the functional characteristics of affinity matured anti-TREM2 antibodies of the present disclosure, would not have been predictable from their improved affinity for TREM2.

[0096] In some embodiments, anti-TREM2 antibodies of the present disclosure have high affinity for TREM2 exhibit the following functional properties: the ability to elevate TREM2 signaling both in soluble and in plate-bound format; the ability to promote survival of primary human

macrophages and primary human dendritic cells; the ability to reduce production of soluble TREM2 (sTREM2) both *in vitro* by primary human myeloid cells and *in vivo*; and have relatively low polyspecific reactivity (PSR), which is a measure of unspecific binding. As disclosed herein, affinity maturation can lead to anti-TREM2 antibody variants that have both increased binding affinity and increased PSR (i.e., relatively high unspecific binding). While certain antibodies of the present disclosure, such as AL2p-31 and AL2p-60, have higher binding affinity and better functional properties than other affinity matured antibody variants, these also exhibit high PSR and have high levels of background binding to cells (*see, e.g.*, **Example 12**). Surprisingly, antibodies AL2p-58 and AL2p-47 exhibit both high binding affinity and relatively low PSR as compared to other high affinity antibody variants, such as AL2p-31 and AL2p-60, while also having the ability to elevate TREM2 signaling both in soluble and in plate-bound format, to promote survival of primary human macrophages and primary human dendritic cells; and to reduce production of soluble TREM2 (sTREM2) both *in vitro* by primary human myeloid cells and *in vivo* (*see, e.g.*, **Examples 2-12**). Based on these results, it was unexpected that antibodies AL2p-58 and AL2p-47 exhibit high affinity to TREM2 and good functional properties without showing any significant PSR or background binding to cells.

[0097] The results in **Example 9** also surprisingly show that affinity matured anti-TREM2 antibodies of the present disclosure, such as AL2p-58 and AL2p-47, induce a several hundred-fold increase in cell viability of primary human macrophages and dendritic cells (*see, e.g.*, **Table 14 and FIG. 8A and 8B**). This functional property is surprising, as affinity matured anti-TREM2 antibodies, such as AL2p-58 and AL2p-47, exhibit only approximately a 10-fold improvement in affinity (K_D) for binding to human TREM2-Fc as compared to the parental mouse anti-TREM2 antibody AL2p (*see, e.g.*, **Tables 1 and 8**), but have a several hundred-fold increase in their ability to promote cell viability. In addition, it is surprising that antibody AL2p-37, which has approximately similar binding affinity than AL2p-58 and AL2p-47, has relatively lower potency than AL2p-58 and AL2p-47 for promoting cell viability.

TREM2 proteins

[0098] In one aspect, the present disclosure provides antibodies that bind to a TREM2 protein of the present disclosure with improved affinity and induce one or more TREM2 activities and/or enhance one or more TREM2 activities after binding to a TREM2 protein expressed in a cell.

[0099] TREM2 proteins of the present disclosure include, without limitation, a human TREM2 protein (Uniprot Accession No. Q9NZC2; SEQ ID NO: 1), and a non-human mammalian TREM2 protein, such as mouse TREM2 protein (Uniprot Accession No. Q99NH8; SEQ ID NO: 2), rat TREM2 protein (Uniprot Accession No. D3ZZ89; SEQ ID NO: 3), Rhesus monkey TREM2 protein (Uniprot Accession No. F6QVF2; SEQ ID NO: 4), cynomolgus monkey TREM2 protein (NCBI Accession No. XP_015304909.1; SEQ ID NO: 5), equine TREM2 protein (Uniprot Accession No.

F7D6L0; SEQ ID NO: 6), pig TREM2 protein (Uniprot Accession No. H2EZZ3; SEQ ID NO: 7), and dog TREM2 protein (Uniprot Accession No. E2RP46; SEQ ID NO: 8). As used herein "TREM2 protein" refers to both wild-type sequences and naturally occurring variant sequences.

[00100] Triggering receptor expressed on myeloid cells-2 (TREM2) is variously referred to as TREM-2, TREM2a, TREM2b, TREM2c, triggering receptor expressed on myeloid cells-2a, and triggering receptor expressed on monocytes-2. TREM2 is a 230 amino acid membrane protein. TREM2 is an immunoglobulin-like receptor primarily expressed on myeloid lineage cells, including without limitation, macrophages, dendritic cells, monocytes, Langerhans cells of skin, Kupffer cells, osteoclasts, and microglia. In some embodiments, TREM2 forms a receptor signaling complex with DAP12. In some embodiments, TREM2 phosphorylates and signals through DAP12 (an ITAM domain adaptor protein). In some embodiments TREM2 signaling results in the downstream activation of PI3K or other intracellular signals. On Myeloid cells, Toll-like receptor (TLR) signals are important for the activation of TREM2 activities, *e.g.*, in the context of an infection response. TLRs also play a key role in the pathological inflammatory response, *e.g.*, TLRs expressed in macrophages and dendritic cells.

[0100] In some embodiments, an example of a human TREM2 amino acid sequence is set forth below as SEQ ID NO: 1:

```
          10         20         30         40         50         60
MEPLRLLILL FVTELSGAHN TTVFQGVAGQ SLQVSCPYDS MKHWGRRKAW CRQLGEKGPC

          70         80         90        100        110        120
QRVVSTHNLW LLSFLRRWNG STAITDDTLG GTLTITLRNL QPHDAGLYQC QSLHGSEADT

         130        140        150        160        170        180
LRKVLVEVLA DPLDHRDAGD LWFPGESESF EDAHVEHSIS RSLLEGEIPF PPTSILLLLA

         190        200        210        220        230
CIFLIKILAA SALWAAAWHG QKPGTHPPSE LDCGHDPGYQ LQTLPGLRDT
```

[0101] In some embodiments, the human TREM2 is a preprotein that includes a signal peptide. In some embodiments, the human TREM2 is a mature protein. In some embodiments, the mature TREM2 protein does not include a signal peptide. In some embodiments, the mature TREM2 protein is expressed on a cell. In some embodiments, TREM2 contains a signal peptide located at amino acid residues 1-18 of human TREM2 (SEQ ID NO: 1); an extracellular immunoglobulin-like variable-type (IgV) domain located at amino acid residues 29-112 of human TREM2 (SEQ ID NO: 1); additional extracellular sequences located at amino acid residues 113-174 of human TREM2 (SEQ ID NO: 1); a transmembrane domain located at amino acid residues 175-195 of human TREM2 (SEQ ID NO: 1); and an intracellular domain located at amino acid residues 196-230 of human TREM2 (SEQ ID NO: 1).

[0102] The transmembrane domain of human TREM2 contains a lysine at amino acid residue 186 that can interact with an aspartic acid in DAP12, which is a key adaptor protein that transduces signaling from TREM2, TREM1, and other related IgV family members.

[0103] Homologues of human TREM2 include, without limitation, the natural killer (NK) cell receptor NK-p44 (NCTR2), the polymeric immunoglobulin receptor (pIgR), CD300E, CD300A, CD300C, and TREML1/TLT1. In some embodiments, NCTR2 has similarity with TREM2 within the IgV domain.

Anti-TREM2 antibodies

[0104] Certain aspects of the present disclosure relate to antibodies (*e.g.*, monoclonal antibodies) that specifically bind to TREM2 with improved affinity. In some embodiments, antibodies of the present disclosure bind a mature TREM2 protein. In some embodiments, antibodies of the present disclosure bind a mature TREM2 protein, wherein the mature TREM2 protein is expressed on a cell. In some embodiments, antibodies of the present disclosure bind a TREM2 protein expressed on one or more human cells selected from human dendritic cells, human macrophages, human monocytes, human osteoclasts, human Langerhans cells of skin, human Kupffer cells, human microglia, and any combinations thereof.

[0105] In some embodiments, anti-TREM2 antibodies of the present disclosure bind to a TREM2 protein without competing with, inhibiting, or otherwise blocking one or more TREM2 ligands from binding to the TREM2 protein. Examples of suitable TREM2 ligands include, without limitation, TREM2 ligands expressed by *E. coli* cells, apoptotic cells, nucleic acids, anionic lipids, APOE, APOE2, APOE3, APOE4, anionic APOE, anionic APOE2, anionic APOE3, anionic APOE4, lipidated APOE, lipidated APOE2, lipidated APOE3, lipidated APOE4, zwitterionic lipids, negatively charged phospholipids, phosphatidylserine, sulfatides, phosphatidylcholin, sphingomyelin, membrane phospholipids, lipidated proteins, proteolipids, lipidated peptides, and lipidated amyloid beta peptide. Accordingly, in certain embodiments, the one or more TREM2 ligands comprise *E. coli* cells, apoptotic cells, nucleic acids, anionic lipids, zwitterionic lipids, negatively charged phospholipids, phosphatidylserine (PS), sulfatides, phosphatidylcholin, sphingomyelin (SM), phospholipids, lipidated proteins, proteolipids, lipidated peptides, and lipidated amyloid beta peptide.

[0106] In some embodiments, anti-TREM2 antibodies of the present disclosure do not inhibit the growth of one or more innate immune cells. In some embodiments, anti-TREM2 antibodies of the present disclosure bind to one or more primary immune cells with an affinity that is from five times higher to 100 times higher 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 comprising 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 embodiments, anti-TREM2 antibodies of the present disclosure bind to one or more primary immune cells with an affinity that is at least five times higher, at least six times higher, at least seven times higher, at least eight times higher, at least nine times higher, at least 10 times higher, at least 11 times higher, at least 12 times higher, at least 13 times higher, at least 14 times higher, at least 15 times higher, at least 16 times higher, at least 17 times higher, at least 18 times higher, at least 19 times higher, at least 20 times higher, at least 21 times higher, at least 22 times higher, at least 23 times higher, at least 24 times higher, at least 25 times higher, at least 26 times higher, at least 27 times higher, at least 28 times higher, at least 29 times higher, at least 30 times higher, at least 35 times higher, at least 40 times higher, at least 45 times higher, at least 50 times higher 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 comprising 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 embodiments, anti-TREM2 antibodies of the present disclosure bind to one or more primary immune cells with a mean fluorescence intensity (MFI) that ranges from 100 to 1500, or greater than 1500. In some embodiments, anti-TREM2 antibodies of the present disclosure bind to one or more primary immune cells with a mean fluorescence intensity (MFI) that is at least 100, at least 110, at least 120, at least 130, at least 140, at least 141, at least 150, at least 152, at least 155, at least 159, at least 160, at least 170, at least 180, at least 187, at least 190, at least 194, at least 195, at least 200, at least 210, at least 220, at least 224, at least 230, at least 235, at least 240, at least 250, at least 260, at least 262, at least 270, at least 280, at least 288, at least 290, at least 296, at least 300, at least 310, at least 318, at least 320, at least 322, at least 327, at least 330, at least 340, at least 350, at least 360, at least 370, at least 372, at least 380, at least 390, at least 400, at least 408, at least 410, at least 413, at least 420, at least 430, at least 440, at least 450, at least 460, at least 470, at least 480, at least 490, at least 499, at least 500, at least 510, at least 520, at least 530, at least 534, at least 540, at least 547, at least 550, at least 560, at least 570, at least 580, at least 590, at least 600, at least 610, at least 620, at least 630, at least 640, at least 650, at least 660, at least 662, at least 670, at least 680, at least 690, at least 700, at least 710, at least 720, at least 730, at least 740, at least 750, at least 760, at least 770, at least 780, at least 790, at least 800, at least 810, at least 820, at least 830, at least 840, at least 850, at least 860, at least 870, at least 880, at least 890, at least 900, at least 910, at least 920, at least 930, at least 940, at least 950, at least 960, at least 970, at least 980, at least 990, at least 1000, at least 1035, at least 1110, at least 1120, at least 1130, at least 1140, at

least 1150, at least 1160, at least 1170, at least 1180, at least 1190, at least 1200, at least 1210, at least 1220, at least 1230, at least 1240, at least 1250, at least 1260, at least 1270, at least 1280, at least 1290, at least 1300, at least 1310, at least 1320, at least 1330, at least 1340, at least 1350, at least 1360, at least 1370, at least 1380, at least 1390, at least 1400, at least 1410, at least 1420, at least 1430, at least 1440, at least 1450, at least 1460, at least 1467, at least 1470, at least 1480, at least 1490, or at least 1500. In some embodiments, the MFI is determined at a temperature of approximately 25°C. In some embodiments, the K_D is determined using a monovalent antibody (*e.g.*, a Fab) or a full-length antibody in a monovalent form. Methods for the preparation and selection of antibodies that interact and/or bind with specificity to TREM2 are described herein. (*e.g.*, see **Examples 1 and 2**).

[0107] In some embodiments, anti-TREM2 antibodies of the present disclosure cluster and activate TREM2 signaling in an amount that is at least 0.5-fold greater, at least 0.6-fold greater, at least 0.7-fold greater, at least 0.8-fold greater, at least 0.9-fold greater, at least 1-fold greater, at least 2-fold greater, at least 3-fold greater, at least 4-fold greater, at least 5-fold greater, at least 6-fold greater, at least 7-fold greater, at least 8-fold greater, at least 9-fold greater, or at least 10-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 comprising 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.

[0108] In some embodiments, anti-TREM2 antibodies of the present disclosure cluster and activate TREM2 signaling in an amount that ranges from about 1-fold over control (FOC) to about 30-fold over control (FOC). In some embodiments, anti-TREM2 antibodies of the present disclosure cluster and activate TREM2 signaling in an amount that is at least 1-fold over control (FOC), at least 1.1-fold over control (FOC), at least 1.2-fold over control (FOC), at least 1.3-fold over control (FOC), at least 1.4-fold over control (FOC), at least 1.5-fold over control (FOC), at least 1.6-fold over control (FOC), at least 1.7-fold over control (FOC), at least 1.8-fold over control (FOC), at least 1.9-fold over control (FOC), at least 2-fold over control (FOC), at least 2.1-fold over control (FOC), at least 2.2-fold over control (FOC), at least 2.3-fold over control (FOC), at least 2.4-fold over control (FOC), at least 2.5-fold over control (FOC), at least 2.6-fold over control (FOC), at least 2.7-fold over control (FOC), at least 2.8-fold over control (FOC), at least 2.9-fold over control (FOC), 3-fold over control

(FOC), at least 3.1-fold over control (FOC), at least 3.2-fold over control (FOC), at least 3.3-fold over control (FOC), at least 3.4-fold over control (FOC), at least 3.5-fold over control (FOC), at least 3.6-fold over control (FOC), at least 3.7-fold over control (FOC), at least 3.8-fold over control (FOC), at least 3.9-fold over control (FOC), 4-fold over control (FOC), at least 4.1-fold over control (FOC), at least 4.2-fold over control (FOC), at least 4.3-fold over control (FOC), at least 4.4-fold over control (FOC), at least 4.5-fold over control (FOC), at least 4.6-fold over control (FOC), at least 4.7-fold over control (FOC), at least 4.8-fold over control (FOC), at least 4.9-fold over control (FOC), 5-fold over control (FOC), at least 5.1-fold over control (FOC), at least 5.2-fold over control (FOC), at least 5.3-fold over control (FOC), at least 5.4-fold over control (FOC), at least 5.5-fold over control (FOC), at least 5.6-fold over control (FOC), at least 5.7-fold over control (FOC), at least 5.8-fold over control (FOC), at least 5.9-fold over control (FOC), 6-fold over control (FOC), at least 6.1-fold over control (FOC), at least 6.2-fold over control (FOC), at least 6.3-fold over control (FOC), at least 6.4-fold over control (FOC), at least 6.5-fold over control (FOC), at least 6.6-fold over control (FOC), at least 6.7-fold over control (FOC), at least 6.8-fold over control (FOC), at least 6.9-fold over control (FOC), 7-fold over control (FOC), at least 7.1-fold over control (FOC), at least 7.2-fold over control (FOC), at least 7.3-fold over control (FOC), at least 7.4-fold over control (FOC), at least 7.5-fold over control (FOC), at least 7.6-fold over control (FOC), at least 7.7-fold over control (FOC), at least 7.8-fold over control (FOC), at least 7.9-fold over control (FOC), 8-fold over control (FOC), at least 8.1-fold over control (FOC), at least 8.2-fold over control (FOC), at least 8.3-fold over control (FOC), at least 8.4-fold over control (FOC), at least 8.5-fold over control (FOC), at least 8.6-fold over control (FOC), at least 8.7-fold over control (FOC), at least 8.8-fold over control (FOC), at least 8.9-fold over control (FOC), 9-fold over control (FOC), at least 9.1-fold over control (FOC), at least 9.2-fold over control (FOC), at least 9.3-fold over control (FOC), at least 9.4-fold over control (FOC), at least 9.5-fold over control (FOC), at least 9.6-fold over control (FOC), at least 9.7-fold over control (FOC), at least 9.8-fold over control (FOC), at least 9.9-fold over control (FOC), at least 10-fold over control (FOC), at least 11-fold over control (FOC), at least 12-fold over control (FOC), at least 13-fold over control (FOC), at least 14-fold over control (FOC), at least 15-fold over control (FOC), at least 16-fold over control (FOC), at least 17-fold over control (FOC), at least 18-fold over control (FOC), at least 19-fold over control (FOC), at least 20-fold over control (FOC), at least 21-fold over control (FOC), at least 22-fold over control (FOC), at least 23-fold over control (FOC), at least 24-fold over control (FOC), at least 25-fold over control (FOC), at least 26-fold over control (FOC), at least 27-fold over control (FOC), at least 28-fold over control (FOC), at least 29-fold over control (FOC), or at least 30-fold over control (FOC). In some embodiments, clustering and activation of TREM2 signaling is determined at 37°C using a monovalent antibody (*e.g.*, a Fab) or a full-length antibody in a monovalent form. Methods for the measuring clustering and activation of TREM2 signaling are described herein (*e.g.*, see **Example 3**).

[0109] In some embodiments, anti-TREM2 antibodies of the present disclosure increase immune cell survival *in vitro* that to an extent that is that is at least one and a half times higher, at least two times higher, at least three times higher, at least four times higher, at least five times higher, at least six times higher, at least seven times higher, at least eight times higher, at least nine times higher, at least 10 times higher, at least 11 times higher, at least 12 times higher, at least 13 times higher, at least 14 times higher, at least 15 times higher, at least 16 times higher, at least 17 times higher, at least 18 times higher, at least 19 times higher, at least 20 times higher, at least 21 times higher, at least 22 times higher, at least 23 times higher, at least 24 times higher, at least 25 times higher, at least 26 times higher, at least 27 times higher, at least 28 times higher, at least 29 times higher, at least 30 times higher, at least 35 times higher, at least 40 times higher, at least 45 times higher, at least 50 times higher, at least 55 times higher, at least 60 times higher, at least 65 times higher, at least 70 times higher, at least 75 times higher, at least 80 times higher, at least 85 times higher, at least 90 times higher, at least 95 times higher, or at least 100 times higher 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 comprising 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.

[0110] In some embodiments, the ability of anti-TREM2 antibodies of the present disclosure to increase immune cell survival *in vitro* is measured by determining the area under the curve (AUC) of growth curves of primary immune cells in culture that were treated with anti-TREM2 antibodies of the present disclosure. In some embodiments, anti-TREM2 antibodies of the present disclosure increase immune cell survival *in vitro* with an AUC that ranges from about 200000 to about 1500000. In some embodiments, anti-TREM2 antibodies of the present disclosure increase immune cell survival *in vitro* with an AUC that is at least 200000, at least 210000, at least 220000, at least 230000, at least 240000, at least 250000, at least 260000, at least 270000, at least 280000, at least 290000, at least 300000, at least 310000, at least 320000, at least 330000, at least 340000, at least 350000, at least 360000, at least 370000, at least 380000, at least 390000, at least 400000, at least 410000, at least 420000, at least 430000, at least 440000, at least 450000, at least 460000, at least 470000, at least 480000, at least 490000, at least 500000, at least 510000, at least 520000, at least 530000, at least 540000, at least 550000, at least 560000, at least 570000, at least 580000, at least 590000, at least 600000, at least 610000, at least 620000, at least 630000, at least 640000, at least 650000, at least 660000, at least 670000, at least 680000, at least 690000, at least 700000, at least 710000, at least 720000, at least 730000, at least 740000, at least 750000, at least 760000, at least 770000, at least 780000, at least 790000, at least 800000, at least 810000, at least 820000, at least 830000, at least

840000, at least 850000, at least 860000, at least 870000, at least 880000, at least 890000, at least 900000, at least 910000, at least 920000, at least 930000, at least 940000, at least 950000, at least 960000, at least 970000, at least 980000, at least 990000, at least 1000000, at least 1010000, at least 1020000, at least 1030000, at least 1040000, at least 1050000, at least 1060000, at least 1070000, at least 1080000, at least 1090000, at least 1100000, at least 1110000, at least 1120000, at least 1130000, at least 1140000, at least 1150000, at least 1160000, at least 1170000, at least 1180000, at least 1190000, at least 1200000, at least 1210000, at least 1220000, at least 1230000, at least 1240000, at least 1250000, at least 1260000, at least 1270000, at least 1280000, at least 1290000, at least 1300000, at least 1310000, at least 1320000, at least 1330000, at least 1340000, at least 1350000, at least 1360000, at least 1370000, at least 1380000, at least 1390000, at least 1400000, at least 1410000, at least 1420000, at least 1430000, at least 1440000, at least 1450000, at least 1460000, at least 1470000, at least 1480000, at least 1490000, or at least 1500000. In some embodiments, immune cell survival *in vitro* is measured at 4°C using a monovalent antibody (*e.g.*, a Fab) or a full-length antibody in a monovalent form. Methods for measuring immune cell survival *in vitro* are described herein (*e.g.*, see **Example 3**).

[0111] In some embodiments, anti-TREM2 antibodies of the present disclosure have an *in vivo* half-life that is lower than a human control IgG1 antibody. In some embodiments, anti-TREM2 antibodies of the present disclosure have an *in vivo* half-life that is at least one and a half times lower, at least two times lower, at least three times lower, at least four times lower, at least five times lower, at least six times lower, at least seven times lower, at least eight times lower, at least nine times lower, at least 10 times lower, at least 11 times lower, at least 12 times lower, at least 13 times lower, at least 14 times lower, at least 15 times lower, at least 16 times lower, at least 17 times lower, at least 18 times lower, at least 19 times lower, at least 20 times lower, at least 21 times lower, at least 22 times lower, at least 23 times lower, at least 24 times lower, at least 25 times lower, at least 26 times lower, at least 27 times lower, at least 28 times lower, at least 29 times lower, at least 30 times lower, at least 35 times lower, at least 40 times lower, at least 45 times lower, at least 50 times lower, at least 55 times lower, at least 60 times lower, at least 65 times lower, at least 70 times lower, at least 75 times lower, at least 80 times lower, at least 85 times lower, at least 90 times lower, at least 95 times lower, or at least 100 times lower 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 comprising 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.

[0112] In some embodiments, anti-TREM2 antibodies of the present disclosure have an *in vivo* half-life that ranges from about 0.1 days to about 10 days. In some embodiments, anti-TREM2 antibodies of the present disclosure have an *in vivo* half-life that is about 0.1 days, about 0.2 days, about 0.3 days, about 0.4 days, about 0.5 days, about 0.6 days, about 0.7 days, about 0.8 days, about 0.9 days, about 1 day, about 1.1 days, about 1.2 days, about 1.3 days, about 1.4 days, about 1.5 days, about 1.6 days, about 1.7 days, about 1.8 days, about 1.9 days, about 2 days, about 2.1 days, about 2.2 days, about 2.3 days, about 2.4 days, about 2.5 days, about 2.6 days, about 2.7 days, about 2.8 days, about 2.9 days, about 3 days, about 3.1 days, about 3.2 days, about 3.3 days, about 3.4 days, about 3.5 days, about 3.6 days, about 3.7 days, about 3.8 days, about 3.9 days, about 4 days, about 4.1 days, about 4.2 days, about 4.3 days, about 4.4 days, about 4.5 days, about 4.6 days, about 4.7 days, about 4.8 days, about 4.9 days, about 5 days, about 5.1 days, about 5.2 days, about 5.3 days, about 5.4 days, about 5.5 days, about 5.6 days, about 5.7 days, about 5.8 days, about 5.9 days, about 6 days, about 6.1 days, about 6.2 days, about 6.3 days, about 6.4 days, about 6.5 days, about 6.6 days, about 6.7 days, about 6.8 days, about 6.9 days, about 7 days, about 7.1 days, about 7.2 days, about 7.3 days, about 7.4 days, about 7.5 days, about 7.6 days, about 7.7 days, about 7.8 days, about 7.9 days, about 8 days, about 8.1 days, about 8.2 days, about 8.3 days, about 8.4 days, about 8.5 days, about 8.6 days, about 8.7 days, about 8.8 days, about 8.9 days, about 9 days, about 9.1 days, about 9.2 days, about 9.3 days, about 9.4 days, about 9.5 days, about 9.6 days, about 9.7 days, about 9.8 days, about 9.9 days, or about 10 days. In some embodiments, *in vivo* half-life is measured using a monovalent antibody (*e.g.*, a Fab) or a full-length antibody in a monovalent form. Methods for measuring *in vivo* half-life are described herein (*e.g.*, see **Example4**).

[0113] Anti-TREM2 antibodies of the present disclosure generally bind with high affinity to one or more TREM2 proteins expressed on a cell. For example, the TREM2 receptor is thought to require clustering on the cell surface in order to transduce a signal. Thus agonist antibodies may have unique features to stimulate, for example, the TREM2 receptor. For example, they may have the correct epitope specificity that is compatible with receptor activation, as well as the ability to induce or retain receptor clustering on the cell surface. In addition, anti-TREM2 antibodies of the present disclosure may display the ability to bind TREM2 without blocking simultaneous binding of one or more TREM2 ligands. The anti-TREM2 antibodies of the present disclosure may further display additive and/or synergistic functional interactions with one or more TREM2 ligands. Thus, in some embodiments, the maximal activity of TREM2 when bound to anti-TREM2 antibodies of the present disclosure in combination with one or more TREM2 ligands of the present disclosure may be greater (*e.g.*, enhanced) than the maximal activity of TREM2 when exposed to saturating concentrations of ligand alone or to saturating concentrations of the antibody alone. In addition, the activity of TREM2 at a given concentration of TREM2 ligand may be greater (*e.g.*, enhanced) in the presence of the antibody. Accordingly, in some embodiments, anti-TREM2 antibodies of the present disclosure have an additive effect with the one or more TREM2 ligands to enhance the one or more TREM2 activities

when bound to the TREM2 protein. In some embodiments, anti-TREM2 antibodies of the present disclosure synergize with the one or more TREM2 ligands to enhance the one or more TREM2 activities. In some embodiments, anti-TREM2 antibodies of the present disclosure increase the potency of the one or more TREM2 ligands to induce the one or more TREM2 activities, as compared to the potency of the one or more TREM2 ligands to induce the one or more TREM2 activities in the absence of the antibody. In some embodiments, anti-TREM2 antibodies of the present disclosure enhance the one or more TREM2 activities in the absence of cell surface clustering of TREM2. In some embodiments, anti-TREM2 antibodies of the present disclosure enhance the one or more TREM2 activities by inducing or retaining cell surface clustering of TREM2. In some embodiments, anti-TREM2 antibodies of the present disclosure are clustered by one or more Fc-gamma receptors expressed on one or more immune cells, including without limitation, B cells and microglial cells. In some embodiments, enhancement of the one or more TREM2 activities induced by binding of one or more TREM2 ligands to the TREM2 protein is measured on primary cells, including without limitation, dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, macrophages, neutrophils, NK cells, osteoclasts, Langerhans cells of skin, and Kupffer cells, or on cell lines, and the enhancement of the one or more TREM2 activities induced by binding of one or more TREM2 ligands to the TREM2 protein is measured, for example, utilizing an *in vitro* cell assay.

[0114] *In vivo*, anti-TREM2 antibodies of the present disclosure may activate receptors by multiple potential mechanisms. In some embodiments, anti-TREM2 antibodies of the present disclosure, have, due to the correct epitope specificity, the ability to activate TREM2 in solution without having to be clustered with a secondary antibody, bound on plates, or clustered through Fcg receptors. In some embodiments, anti-TREM2 antibodies of the present disclosure have isotypes of human antibodies, such as IgG2, that have, due to their unique structure, an intrinsic ability to cluster receptors or retain receptors in a clustered configuration, thereby activating receptors such as TREM2 without binding to an Fc receptor (*e.g.*, White et al., (2015) Cancer Cell 27, 138–148).

[0115] In some embodiments, anti-TREM2 antibodies of the present disclosure cluster receptors (*e.g.*, TREM2) by binding to Fcg receptors on adjacent cells. Binding of the constant IgG Fc part of the antibody to Fcg receptors leads to aggregation of the antibodies, and the antibodies in turn aggregate the receptors to which they bind through their variable region (Chu et al (2008) Mol Immunol, 45:3926-3933; and Wilson et al., (2011) Cancer Cell 19, 101–113). Binding to the inhibitory Fcg receptor FcgR (FcgRIIB) that does not elicit cytokine secretion, oxidative burst, increased phagocytosis, and enhanced antibody-dependent, cell-mediated cytotoxicity (ADCC) is often a preferred way to cluster antibodies *in vivo*, since binding to FcgRIIB is not associated with immune adverse effects. Any suitable assay described herein may be used to determine antibody clustering.

[0116] Other mechanisms may also be used to cluster receptors (*e.g.*, TREM2). For example, in some embodiments, antibody fragments (*e.g.*, Fab fragments) that are cross-linked together may be

used to cluster receptors (*e.g.*, TREM2) in a manner similar to antibodies with Fc regions that bind Fcg receptors, as described above. In some embodiments, cross-linked antibody fragments (*e.g.*, Fab fragments) may function as agonist antibodies if they induce receptor clustering on the cell surface and bind an appropriate epitope on the target (*e.g.*, TREM2).

[0117] In some embodiments, antibodies of the present disclosure that bind a TREM2 protein may include antibodies that due to their epitope specificity bind TREM2 and activate one or more TREM2 activities. In some embodiments, such antibodies may bind to the ligand-binding site on TREM2 and mimic the action of one or more TREM2 ligands, or stimulate the target antigen to transduce signal by binding to one or more domains that are not the ligand-binding sites. In some embodiments, the antibodies do not compete with or otherwise block ligand binding to TREM2. In some embodiments, the antibodies, act additively or synergistically with one or more TREM2 ligands to activate and/or enhance one more TREM2 activities.

[0118] In some embodiments, TREM2 activities that may be induced and/or enhanced by anti-TREM2 antibodies of the present disclosure and/or one or more TREM2 ligands of the present disclosure include, without limitation, TREM2 binding to DAP12; DAP12 phosphorylation; activation of Syk kinase; modulation of one or more pro-inflammatory mediators selected from IFN-β, IL-1α, IL-1β, TNF-α, IL-6, IL-8, CRP, CD86, MCP-1/CCL2, CCL3, CCL4, CCL5, CCR2, CXCL-10, Gata3, IL-20 family members, IL-33, LIF, IFN-gamma, OSM, CNTF, CSF-1, OPN, CD11c, GM-CSF, IL-11, IL-12, IL-17, IL-18, and IL-23, where the modulation may occurs in one or more cells selected from macrophages, M1 macrophages, activated M1 macrophages, M2 macrophages, dendritic cells, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, and microglial cells; recruitment of Syk to a DAP12/TREM2 complex; increasing activity of one or more TREM2-dependent genes, where the one or more TREM2-dependent genes comprise nuclear factor of activated T-cells (NFAT) transcription factors; increased survival of dendritic cells, macrophages, M1 macrophages, activated M1 macrophages, M2 macrophages, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, microglia, M1 microglia, activated M1 microglia, and M2 microglia, or any combination thereof; modulated expression of one or more stimulatory molecules selected from CD83, CD86 MHC class II, CD40, and any combination thereof, where the CD40 may be expressed on dendritic cells, monocytes, macrophages, or any combination thereof, and where the dendritic cells may comprise bone marrow-derived dendritic cells; increasing memory; and reducing cognitive deficit.

[0119] As used herein, an anti-TREM2 antibody of the present disclosure enhances one or more TREM2 activities induced by binding of one or more TREM2 ligands to the TREM2 protein if it induces at least a 2-fold, at least a 3-fold, at least a 4-fold, at least a 5-fold, at least a 6-fold, at least a 7-fold, at least a 8-fold, at least a 9-fold, at least a 10-fold, at least an 11-fold, at least a 12-fold, at least a 13-fold, at least a 14-fold, at least a 15-fold, at least a 16-fold, at least a 17-fold, at least an 18-fold, at least a 19-fold, at least a 20-fold or greater increase in the one or more TREM2 activities as

compared to levels of the one or more TREM2 activities induced by binding of one or more TREM2 ligands to the TREM2 protein in the absence of the anti-TREM2 antibody. In some embodiments, the increase in one more TEM2 activities may be measured by any suitable *in vitro* cell-based assays or suitable *in vivo* model described herein or known in the art, for example, by utilizing a luciferase-based reporter assay to measure TREM2-dependent gene expression, using Western blot analysis to measure increase in TREM2-induced phosphorylation of downstream signaling partners, such as Syk, or by utilizing flow cytometry, such as fluorescence-activated cell sorting (FACS) to measure changes in cell surface levels of markers of TREM2 activation. Any *in vitro* cell-based assays or suitable *in vivo* model described herein or known in the art may be used to measure interaction (*e.g.*, binding) between TREM2 and one or more TREM2 ligands.

[0120] In some embodiments an anti-TREM2 antibody of the present disclosure enhances one or more TREM2 activities induced by binding of a TREM2 ligand to the TREM2 protein if it induces an increase that ranges from about 1-fold to about 6-fold, or more than 6-fold in ligand-induced TREM2-dependent gene transcription when used at a concentration that ranges from about 0.5 nM to about 50 nM, or greater than 50 nM, and as compared to the level of TREM2-dependent gene transcription induced by binding of the TREM2 ligand to the TREM2 protein in the absence of the anti-TREM2 antibody when the TREM2 ligand is used at its EC_{50} concentration. In some embodiments the increase in ligand-induced TREM2-dependent gene transcription is at least 1-fold, at least 2-fold, at least a 3-fold, at least a 4-fold, at least a 5-fold, at least a 6-fold, at least a 7-fold, at least a 8-fold, at least a 9-fold, at least a 10-fold, at least an 11-fold, at least a 12-fold, at least a 13-fold, at least a 14-fold, at least a 15-fold, at least a 16-fold, at least a 17-fold, at least an 18-fold, at least a 19-fold, at least a 20-fold or greater when used at a concentration that ranges from about 0.5 nM to about 50 nM, or greater than 50 nM, and as compared to the level of TREM2-dependent gene transcription induced by binding of the TREM2 ligand to the TREM2 protein in the absence of the anti-TREM2 antibody when the TREM2 ligand is used at its EC_{50} concentration. In some embodiments, the anti-TREM2 antibody is used at a concentration of at least 0.5 nM, at least 0.6 nM, at least 0.7 nM, at least 0.8 nM, at least 0.9 nM, at least 1 nM, at least 2 nM, at least 3 nM, at least 4 nM, at least 5 nM, at least 6 nM, at least 7 nM, at least 8 nM, at least 9 nM, at least 10 nM, at least 15 nM, at least 20 nM, at least 25 nM, at least 30 nM, at least 35 nM, at least 40 nM, at least 45 nM, at least 46 nM, at least 47 nM, at least 48 nM, at least 49 nM, or at least 50 nM. In some embodiments, the TREM2 ligand is phosphatidylserine (PS). In some embodiments, the TREM2 ligand is sphingomyelin (SM). In some embodiments, the increase in one more TEM2 activities may be measured by any suitable *in vitro* cell-based assays or suitable *in vivo* model described herein or known in the art. In some embodiments, a luciferase-based reporter assay is used to measure the fold increase of ligand-induced TREM2-dependent gene expression in the presence and absence of antibody.

[0121] As used herein, an anti-TREM2 antibody of the present disclosure does not compete with, inhibit, or otherwise block the interaction (*e.g.*, binding) between one or more TREM2 ligands and

TREM2 if it decreases ligand binding to TREM2 by less than 20% at saturating antibody concentrations utilizing any *in vitro* assay or cell-based culture assay described herein or known in the art. In some embodiments, anti-TREM2 antibodies of the present disclosure inhibit interaction (*e.g.*, binding) between one or more TREM2 ligands and TREM2 by less than 20%, less than 19%, less than 18%, less than 17%, less than 16%, less than 15%, less than 14%, less than 13%, less than 12%, less than 11%, less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, or less than 1% at saturating antibody concentrations utilizing any *in vitro* assay or cell-based culture assay described herein or known in the art.

[0122] In some embodiments, an anti-TREM2 antibody of the present disclosure induces one or more TREM2 activities. In some embodiments, the antibody induces one or more activities of TREM2 after binding to a TREM2 protein that is expressed on a cell. In some embodiments, the antibody induces one or more activities of TREM2 after binding to a soluble TREM2 protein that is not bound to the cell membrane. In certain embodiments, the TREM2 protein is expressed on a cell surface. In certain embodiments, soluble TREM2 protein (sTREM2) may be found, without limitation, in extracellular milieu, in blood serum, in cerebrospinal fluid (CSF), and in the interstitial space within tissues. In certain embodiments, soluble TREM2 protein (sTREM2) is non-cellular. In some embodiments a soluble TREM2 (sTREM2) protein of the present disclosure corresponds to amino acid residues 19-160 of SEQ ID NO:1. In some embodiments a soluble TREM2 (sTREM2) protein of the present disclosure corresponds to amino acid residues 19-159 of SEQ ID NO:1. In some embodiments a soluble TREM2 (sTREM2) protein of the present disclosure corresponds to amino acid residues 19-158 of SEQ ID NO:1. In some embodiments a soluble TREM2 (sTREM2) protein of the present disclosure corresponds to amino acid residues 19-157 of SEQ ID NO:1. In some embodiments a soluble TREM2 (sTREM2) protein of the present disclosure corresponds to amino acid residues 19-156 of SEQ ID NO:1. In some embodiments a soluble TREM2 (sTREM2) protein of the present disclosure corresponds to amino acid residues 19-155 of SEQ ID NO:1. In some embodiments a soluble TREM2 (sTREM2) protein of the present disclosure corresponds to amino acid residues 19-154 of SEQ ID NO:1.

[0123] In some embodiments, soluble TREM2 (sTREM2) proteins of the present disclosure may be inactive variants of cellular TREM2 receptors. In some embodiments, sTREM2 may be present in the periphery, such as in the plasma, or brains of subject.

[0124] In some embodiments, anti-TREM2 antibodies of the present disclosure decrease plasma levels of soluble TREM2 *in vivo*. In some embodiments, anti-TREM2 antibodies of the present disclosure decrease plasma levels of soluble TREM2 *in vivo* by blocking cleavage, by inhibiting one or more metalloproteases, or by inducing internalization.

[0125] In some embodiments, anti-TREM2 antibodies of the present disclosure decrease plasma levels of soluble TREM2 *in vivo* by an amount that ranges from about 5% greater to about 50% greater than that of a human control IgG1 antibody. In some embodiments, anti-TREM2 antibodies of

the present disclosure decreases plasma levels of soluble TREM2 *in vivo* by an amount that is at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, or at least 50% greater than that of a human control IgG1 antibody.

[0126] In some embodiments, anti-TREM2 antibodies of the present disclosure decrease plasma levels of soluble TREM2 *in vivo* such that the plasma level of soluble TREM2 as a percentage of baseline six days of after antibody treatment is at least 5%, at least 6%, at least 7%, at least 8%, at least 9%,at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, or at least 80%. In some embodiments, plasma levels of soluble TREM2 *in vivo* are measured using a monovalent antibody (*e.g.*, a Fab) or a full-length antibody in a monovalent form. Methods for measuring plasma levels of soluble TREM2 *in vivo* are described herein (*e.g.*, see **Example4**).

[0127] Anti-TREM2 antibodies of the present disclosure can be used to prevent, reduce risk of, or treat dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, tauopathy disease, Nasu-Hakola disease, stroke, acute trauma, chronic trauma, cognitive deficit, memory loss, lupus, acute and chronic colitis, rheumatoid arthritis, wound healing, Crohn's disease, inflammatory bowel disease, ulcerative colitis, obesity, malaria, essential tremor, central nervous system lupus, Behcet's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, Shy-Drager syndrome, progressive supranuclear palsy, cortical basal ganglionic degeneration, acute disseminated encephalomyelitis, granulomartous disorders, sarcoidosis, diseases of aging, seizures, spinal cord injury, traumatic brain injury, age related macular degeneration, glaucoma, retinitis pigmentosa, retinal degeneration, respiratory tract infection, sepsis, eye infection, systemic infection, lupus, arthritis, multiple sclerosis, low bone density, osteoporosis, osteogenesis, osteopetrotic disease, Paget's disease of bone, solid and blood cancer, bladder cancer,

brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, polycythemia vera, essential thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express TREM2, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza. The methods provided herein also find use in inducing or promoting the survival, maturation, functionality, migration, or proliferation of one or more immune cells in an individual in need thereof. The methods provided herein find further use in decreasing the activity, functionality, or survival of regulatory T cells, tumor-imbedded immunosuppressor dendritic cells, tumor-imbedded immunosuppressor macrophages, myeloid-derived suppressor cells, tumor-associated macrophages, acute myeloid leukemia (AML) cells, chronic lymphocytic leukemia (CLL) cell, or chronic myeloid leukemia (CML) cell in an individual in need thereof. The methods provided herein find further use in increasing memory and/or reducing cognitive deficit.

[0128] The anti-TREM2 antibodies of the present disclosure may also be used in advanced wound care. In some embodiments, the anti-TREM2 antibodies of the present disclosure are monoclonal antibodies. Anti-TREM2 antibodies of the present disclosure may be tested for inducing one or more TREM2 activities. Useful assays may include western blots (*e.g.*, for tyrosine-phosphorylated DAP12 or threonine/serine-phosphorylated PI3K-kinase substrates), ELISA (*e.g.*, for secreted interleukin or cytokine secretion), FACS (*e.g.*, for anti-TREM2 binding to TREM2), immunocytochemistry (*e.g.*, for *e.g.*, for tyrosine-phosphorylated DAP12 or threonine/serine-phosphorylated PI3K-kinase substrates), reporter-gene assays (*e.g.*, for TLR activation), increased survival and/or function of dendritic cells, macrophages, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or microglia, increased phagocytosis of apoptotic neurons, damaged synapses, amyloid beta or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, 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, and proline-arginine (PR) repeat peptides, nerve tissue debris, non-nerve tissue debris, bacteria, other foreign bodies, disease-causing proteins, disease-causing peptides, disease-causing nucleic acid, or tumor cells by macrophages, dendritic cells, Langerhans cells of skin, Kupffer cells, monocytes, osteoclasts, and/or microglial cells, increased

cytoskeleton reorganization, and decreased microglial pro-inflammatory responses, or other assays known in the art.

[0129] An antibody dependent on binding to FcgR receptor to activate targeted receptors may lose its agonist activity if engineered to eliminate FcgR binding (see, *e.g.*, Wilson et al., (2011) Cancer Cell 19, 101–113; Armour at al., (2003) Immunology 40 (2003) 585–593); and White et al., (2015) Cancer Cell 27, 138–148). As such, it is thought that an anti-TREM2 antibody of the present disclosure with the correct epitope specificity can activate the target antigen, with minimal adverse effects, when the antibody has an Fc domain from a human IgG2 isotype (CH1 and hinge region) or another type of Fc domain that is capable of preferentially binding the inhibitory FcgRIIB r receptors, or a variation thereof.

[0130] Exemplary antibody Fc isotypes and modifications are provided in Table A below. In some embodiments, the antibody has an Fc isotype listed in Table A below.

Table A: Exemplary antibody Fc isotypes that are capable of binding Fc gamma receptor

Fc Isotype	**Mutation (EU numbering scheme)**
IgG1	N297A
IgG1	D265A and N297A
IgG1	D270A
IgG1	L234A and L235A L234A and G237A L234A and L235A and G237A
IgG1	P238D and/or L328E and/or S267E/L328F and/or E233 and or/ G237D and/or H268D and/or P271G and/or A330R
IgG1	P238D and L328E and E233D and G237D and H268D and P271G and A330R
IgG1	P238D and L328E and G237D and H268D and P271G and A330R
IgG1	P238D and S267E and L328F and E233D and G237D and H268D and P271G and A330R
IgG1	P238D and S267E and L328F and G237D and H268D and P271G and A330R
IgG2	V234A and G237A
IgG4	L235A and G237A and E318A
IgG4	S228P and L236E
IgG2/4 hybrid	IgG2 aa 118 to 260 and IgG4 aa 261 to 447
	H268Q and V309L; and A330S and P331S
IgG1	C226S and C229S and E233P and L234V and L235A
IgG1	L234F and L235E and P331S
IgG2	C232S or C233S
IgG2	A330S and P331S
IgG1	S267E, and L328F S267E alone
IgG2	S267E and L328F
IgG4	S267E and L328F
IgG2	WT HC with Kappa (light chain) LC HC C127S with Kappa LC Kappa LC C214S

Fc Isotype	Mutation (EU numbering scheme)
	Kappa LC C214S and HC C233S Kappa LC C214S and HC C232S Any of the above listed mutations together with A330S and P331S mutations F(ab`)2 fragment of WT IgG1 and any of the above listed mutations
IgG1	Substitute the Constant Heavy 1 (CH1) and hinge region of IgG1 With CH1 and hinge region of IGg2 ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSNFGTQT YTCNVDHKPS NTKVDKTVER KCCVECPPCP (SEQ ID NO: 145) With a Kappa LC
IgG1	Any of the above listed mutations together with A330L/A330S and/ or L234F and/or L235E and/or P331S
IgG1, IgG2, or IgG4	Any of the above listed mutations together with M252Y and/or S254T and/or T256E
Mouse IgG1	For mouse disease models
IgG4	WT
IgG1	Any of the above listed mutation together with E430G, E430S, E430F, E430T, E345K, E345Q, E345R, E345Y, S440Y, S440W and/or any combination thereof.
IgG2	Any of the above listed mutation together with E430G, E430S, E430F, E430T, E345K, E345Q, E345R, E345Y, S440Y, S440W and/or any combination thereof.

[0131] In addition to the isotypes described in Table A, and without wishing to be bound to theory, it is thought that antibodies with human IgG1 or IgG3 isotypes and mutants thereof (*e.g.* Strohl (2009) Current Opinion in Biotechnology 2009, 20:685–691) that bind the activating Fcg Receptors I, IIA, IIC, IIIA, IIIB in human and/or Fcg Receptors I, III and IV in mouse, may also act as agonist antibodies in vivo but may be associated with adverse effects related to ADCC. However, such Fcg receptors appear to be less available for antibody binding in vivo, as compared to the Inhibitory Fcg receptor FcgRIIB (see, *e.g.*, White, et al., (2013) Cancer Immunol. Immunother. 62, 941–948; and Li et al., (2011) Science 333(6045):1030–1034.).

[0132] In some embodiments, the antibody is of the IgG class, the IgM class, or the IgA class. In some embodiments, the antibody has an IgG1, IgG2, IgG3, or IgG4 isotype.

[0133] In certain embodiments, the antibody has an IgG2 isotype. In some embodiments, the antibody contains a human IgG2 constant region. In some embodiments, the human IgG2 constant region includes an Fc region. In some embodiments, the antibody induces the one or more TREM2 activities, the DAP12 activities, or both independently of binding to an Fc receptor. In some embodiments, the antibody binds an inhibitory Fc receptor. In certain embodiments, the inhibitory Fc receptor is inhibitory Fc-gamma receptor IIB (FcγIIB). In some embodiments, the Fc region contains one or more modifications. For example, in some embodiments, the Fc region contains one or more

amino acid substitutions (*e.g.*, relative to a wild-type Fc region of the same isotype). In some embodiments, the one or more amino acid substitutions are selected from V234A (Alegre et al., (1994) *Transplantation* 57:1537-1543. 31; Xu et al., (2000) *Cell Immunol*, 200:16-26), G237A (Cole et al. (1999) *Transplantation*, 68:563-571), H268Q, V309L, A330S, P331S (US 2007/0148167; Armour et al. (1999) *Eur J Immunol* 29: 2613-2624; Armour et al. (2000) *The Haematology Journal* 1(Suppl.1):27; Armour et al. (2000) *The Haematology Journal* 1(Suppl.1):27), C232S, and/or C233S (White et al., (2015) *Cancer Cell* 27, 138–148), S267E, L328F (Chu et al., (2008) *Mol Immunol*, 45:3926-3933), M252Y, S254T, and/or T256E, where the amino acid position is according to the EU or, Kabat numbering convention.

[0134] In some embodiments, the antibody has an IgG2 isotype with a heavy chain constant domain that contains a C127S amino acid substitution, where the amino acid position is according to the EU or, Kabat numbering convention (White et al., (2015) *Cancer Cell* 27, 138-148; Lightle et al., (2010) *PROTEIN SCIENCE* 19:753-762; and WO2008079246).

[0135] In some embodiments, the antibody has an IgG2 isotype with a Kappa light chain constant domain that contains a C214S amino acid substitution, where the amino acid position is according to the EU or, Kabat numbering convention (White et al.,(2015) *Cancer Cell* 27, 138-148; Lightle et al., (2010) *PROTEIN SCIENCE* 19:753-762; and WO2008079246).

[0136] In certain embodiments, the antibody has an IgG1 isotype. In some embodiments, the antibody contains a mouse IgG1 constant region. In some embodiments, the antibody contains a human IgG1 constant region. In some embodiments, the human IgG1 constant region includes an Fc region. In some embodiments, the antibody binds an inhibitory Fc receptor. In certain embodiments, the inhibitory Fc receptor is inhibitory Fc-gamma receptor IIB (FcγIIB). In some embodiments, the Fc region contains one or more modifications. For example, in some embodiments, the Fc region contains one or more amino acid substitutions (*e.g.*, relative to a wild-type Fc region of the same isotype). In some embodiments, the one or more amino acid substitutions are selected from N297A (Bolt S et al. (1993) *Eur J Immunol* 23:403-411), D265A (Shields et al. (2001) *R. J. Biol. Chem.* 276, 6591–6604), L234A, L235A (Hutchins et al. (1995) *Proc Natl Acad Sci* USA, 92:11980-11984; Alegre et al., (1994) *Transplantation* 57:1537-1543. 31; Xu et al., (2000) *Cell Immunol*, 200:16-26), G237A (Alegre et al. (1994) *Transplantation* 57:1537-1543. 31; Xu et al. (2000) *Cell Immunol*, 200:16-26),C226S, C229S, E233P, L234V, L234F, L235E (McEarchern et al., (2007) *Blood*, 109:1185-1192), P331S (Sazinsky et al., (2008) *Proc Natl Acad Sci USA* 2008, 105:20167-20172), S267E, L328F, A330L, M252Y, S254T, and/or T256E, where the amino acid position is according to the EU or, Kabat numbering convention.

[0137] In some embodiments, the antibody includes an IgG2 isotype heavy chain constant domain 1(CH1) and hinge region (White et al., (2015) Cancer Cell 27, 138–148). In certain embodiments, the IgG2 isotype CH1 and hinge region contain the amino acid sequence of ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY

SLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCP (SEQ ID NO: 145). In some embodiments, the antibody Fc region contains a S267E amino acid substitution, a L328F amino acid substitution, or both, and/or a N297A or N297Q amino acid substitution, where the amino acid position is according to the EU or, Kabat numbering convention.

[0138] In certain embodiments, the antibody has an IgG4 isotype. In some embodiments, the antibody contains a human IgG4 constant region. In some embodiments, the human IgG4 constant region includes an Fc region. In some embodiments, the antibody binds an inhibitory Fc receptor. In certain embodiments, the inhibitory Fc receptor is inhibitory Fc-gamma receptor IIB (FcγIIB). In some embodiments, the Fc region contains one or more modifications. For example, in some embodiments, the Fc region contains one or more amino acid substitutions (*e.g.*, relative to a wild-type Fc region of the same isotype). In some embodiments, the one or more amino acid substitutions are selected from L235A, G237A, S228P, L236E (Reddy et al., (2000) *J Immunol*,164:1925-1933), S267E, E318A, L328F, M252Y, S254T, and/or T256E, where the amino acid position is according to the EU or, Kabat numbering convention.

[0139] In certain embodiments, the antibody has a hybrid IgG2/4 isotype. In some embodiments, the antibody includes an amino acid sequence containing amino acids 118 to 260 according to EU or, Kabat numbering of human IgG2 and amino acids 261-447 according to EU or, Kabat numbering of human IgG4 (WO 1997/11971; WO 2007/106585).

[0140] In certain embodiments, the antibody contains a mouse IgG4 constant region (Bartholomaeus, et al. (2014). J. Immunol. 192, 2091–2098).

[0141] In some embodiments, the Fc region further contains one or more additional amino acid substitutions selected from A330L, L234F; L235E, or P331S according to EU or, Kabat numbering; and any combination thereof.

[0142] In certain embodiments, the antibody contains one or more amino acid substitutions in the Fc region at a residue position selected from C127S, L234A, L234F, L235A, L235E, S267E, K322A, L328F, A330S, P331S, E345R, E430G, S440Y, and any combination thereof, where the numbering of the residues is according to EU or Kabat numbering. In some embodiments, the Fc region contains an amino acid substitution at positions E430G, L243A, L235A, and P331S, where the numbering of the residue position is according to EU numbering. In some embodiments, the Fc region contains an amino acid substitution at positions E430G and P331S, where the numbering of the residue position is according to EU numbering. In some embodiments, the Fc region contains an amino acid substitution at positions E430G and K322A, where the numbering of the residue position is according to EU numbering. In some embodiments, the Fc region contains an amino acid substitution at positions E430G, A330S, and P331S, where the numbering of the residue position is according to EU numbering. In some embodiments, the Fc region contains an amino acid substitution at positions E430G, K322A, A330S, and P331S, where the numbering of the residue position is according to EU numbering. In some embodiments, the Fc region contains an amino acid substitution at positions

E430G, K322A, and A330S, where the numbering of the residue position is according to EU numbering. In some embodiments, the Fc region contains an amino acid substitution at positions E430G, K322A, and P331S, where the numbering of the residue position is according to EU numbering. In some embodiments, the Fc region contains an amino acid substitution at positions S267E and L328F, where the numbering of the residue position is according to EU numbering. In some embodiments, the Fc region contains an amino acid substitution at position C127S, where the numbering of the residue position is according to EU numbering. In some embodiments, the Fc region contains an amino acid substitution at positions E345R, E430G and S440Y, where the numbering of the residue position is according to EU numbering.

Further IgG mutations

[0143] In some embodiments, one or more of the IgG1 variants described herein may be combined with an A330L mutation (Lazar et al., (2006) Proc Natl Acad Sci USA, 103:4005-4010), or one or more of L234F, L235E, and/or P331S mutations (Sazinsky et al., (2008) Proc Natl Acad Sci USA, 105:20167-20172), where the amino acid position is according to the EU or, Kabat numbering convention, to eliminate complement activation. In some embodiments, the IgG variants described herein may be combined with one or more mutations to enhance the antibody half-life in human serum (*e.g.* M252Y, S254T,T256E mutations according to the EU or, Kabat numbering convention) (Dall'Acqua et al., (2006) J Biol Chem, 281:23514-23524; and Strohl e al., (2009) Current Opinion in Biotechnology, 20:685–691).

[0144] In some embodiments, an IgG4 variant of the present disclosure may be combined with an S228P mutation according to the EU or, Kabat numbering convention (Angal et al., (1993) Mol Immunol, 30:105-108) and/or with one or more mutations described in Peters et al., (2012) J Biol Chem. 13;287(29):24525-33) to enhance antibody stabilization.

Exemplary anti-TREM2 antibodies

[0145] In some embodiments, an isolated anti-TREM2 antibody of the present disclosure binds to TREM2 with high affinity and enhances one or more TREM2 activities induced by binding of one or more TREM2 ligands to the TREM2 protein, as compared to the one or more TREM2 activities induced by binding of the one or more TREM2 ligands to the TREM2 protein in the absence of the isolated antibody. In some embodiments, the anti-TREM2 antibody enhances the one or more TREM2 activities without competing with or otherwise blocking binding of the one or more TREM2 ligands to the TREM2 protein. In some embodiments, the antibody is a humanized antibody, a bispecific antibody, a multivalent antibody, or a chimeric antibody. Exemplary descriptions of such antibodies are found throughout the present disclosure. In some embodiments, the antibody is a bispecific antibody recognizing a first antigen and a second antigen.

[0146] In some embodiments, anti-TREM2 antibodies of the present disclosure bind to a human TREM2, or a homolog thereof, including without limitation a mammalian (*e.g.*, non-human mammalian) TREM2 protein, mouse TREM2 protein (Uniprot Accession No. Q99NH8), rat TREM2

protein (Uniprot Accession No. D3ZZ89), Rhesus monkey TREM2 protein (Uniprot Accession No. F6QVF2), cynomolgus monkey TREM2 protein (NCBI Accession No. XP_015304909.1), equine TREM2 protein (Uniprot Accession No. F7D6L0), pig TREM2 protein (Uniprot Accession No. H2EZZ3), and dog TREM2 protein (Uniprot Accession No. E2RP46). In some embodiments, anti-TREM2 antibodies of the present disclosure specifically bind to human TREM2. In some embodiments, anti-TREM2 antibodies of the present disclosure specifically bind to cynomolgus monkey TREM2. In some embodiments, anti-TREM2 antibodies of the present disclosure specifically bind to both human TREM2 and cynomolgus monkey TREM2. In some embodiments, anti-TREM2 antibodies of the present disclosure induce at least one TREM2 activity of the present disclosure.

Anti-TREM2 antibody-binding regions

[0147] Certain aspects of the preset disclosure relate to anti-TREM2 antibodies that bind to an epitope of human TREM2 that is the same as or overlaps with the TREM2 epitope bound by 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 embodiments, anti-TREM2 antibodies of the present disclosure bind essentially the same TREM2 epitope bound by 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 embodiments, anti-TREM2 antibodies of the present disclosure bind to one or more amino acids within amino acid residues SFEDAHVEH (amino acid residues 149-157 of SEQ ID NO: 1). In some embodiments, anti-TREM2 antibodies of the present disclosure bind to one or more amino acid residues selected from E151, D152, and E156 of SEQ ID NO: 1. In some embodiments, anti-TREM2 antibodies of the present disclosure bind amino acid residues E151, D152, and E156 of SEQ ID NO: 1.

[0148] In some embodiments, anti-TREM2 antibodies of the present disclosure competitively inhibit binding of 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 embodiments, anti-TREM2 antibodies of the present disclosure compete with 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 for binding to TREM2.

[0149] In some embodiments, anti-TREM2 antibodies of the present disclosure competitively inhibit binding of at least one antibody selected from any of the antibodies listed in **Tables 2A-2C, 3A-3C, 4A-4D, 5A-5D, 6, and 7**. In some embodiments, anti-TREM2 antibodies of the present disclosure competitively inhibit binding of at least one antibody selected from 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 embodiments, anti-TREM2 antibodies of the present disclosure competitively inhibit binding of antibody AL2p-31. In some embodiments, anti-TREM2 antibodies of the present disclosure competitively inhibit binding of antibody AL2p-37. In some embodiments, anti-TREM2 antibodies of the present disclosure competitively inhibit binding of antibody AL2p-47. In some embodiments, anti-TREM2 antibodies of the present disclosure competitively inhibit binding of antibody AL2p-58. In some embodiments, anti-TREM2 antibodies of the present disclosure competitively inhibit binding of antibody AL2p-60. In some embodiments, anti-TREM2 antibodies of the present disclosure competitively inhibit binding of antibody AL2p-61. In some embodiments, anti-TREM2 antibodies of the present disclosure competitively inhibit binding of antibody AL2p-62.

[0150] In some embodiments, anti-TREM2 antibodies of the present disclosure bind to an epitope of human TREM2 that is the same as or overlaps with the TREM2 epitope bound by at least one antibody selected from any of the antibodies listed in **Tables 2A-2C, 3A-3C, 4A-4D, 5A-5D, 6, and 7**. In some embodiments, anti-TREM2 antibodies of the present disclosure bind to an epitope of human TREM2 that is the same as or overlaps with the TREM2 epitope bound by at least one antibody selected from 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 embodiments, anti-TREM2 antibodies of the present disclosure bind to an epitope of human TREM2 that is the same as or overlaps with the TREM2 epitope bound by antibody AL2p-31. In some embodiments, anti-TREM2 antibodies of the present disclosure bind to an epitope of human TREM2 that is the same as or overlaps with the TREM2 epitope bound by antibody AL2p-37. In some embodiments, anti-TREM2 antibodies of the present disclosure bind to an epitope of human TREM2 that is the same as or overlaps with the TREM2 epitope bound by antibody AL2p-47. In some embodiments, anti-TREM2 antibodies of the present disclosure bind to an epitope of human TREM2 that is the same as or overlaps with the

TREM2 epitope bound by antibody AL2p-58. In some embodiments, anti-TREM2 antibodies of the present disclosure bind to an epitope of human TREM2 that is the same as or overlaps with the TREM2 epitope bound by antibody AL2p-60. In some embodiments, anti-TREM2 antibodies of the present disclosure bind to an epitope of human TREM2 that is the same as or overlaps with the TREM2 epitope bound by antibody AL2p-61. In some embodiments, anti-TREM2 antibodies of the present disclosure bind to an epitope of human TREM2 that is the same as or overlaps with the TREM2 epitope bound by antibody AL2p-62.

[0151] In some embodiments, anti-TREM2 antibodies of the present disclosure bind essentially the same TREM2 epitope bound by at least one antibody selected from any of the antibodies listed in **Tables 2A-2C, 3A-3C, 4A-4D, 5A-5D, 6, and 7**. In some embodiments, anti-TREM2 antibodies of the present disclosure bind essentially the same TREM2 epitope bound by at least one antibody selected from 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. Detailed exemplary methods for mapping an epitope to which an antibody binds are provided in Morris (1996) "Epitope Mapping Protocols," in *Methods in Molecular Biology* vol. 66 (Humana Press, Totowa, NJ). In some embodiments, anti-TREM2 antibodies of the present disclosure bind essentially the same TREM2 epitope bound by antibody AL2p-31. In some embodiments, anti-TREM2 antibodies of the present disclosure bind essentially the same TREM2 epitope bound by antibody AL2p-37. In some embodiments, anti-TREM2 antibodies of the present disclosure bind essentially the same TREM2 epitope bound by antibody AL2p-47. In some embodiments, anti-TREM2 antibodies of the present disclosure bind essentially the same TREM2 epitope bound by antibody AL2p-58. In some embodiments, anti-TREM2 antibodies of the present disclosure bind essentially the same TREM2 epitope bound by antibody AL2p-60. In some embodiments, anti-TREM2 antibodies of the present disclosure bind essentially the same TREM2 epitope bound by antibody AL2p-61. In some embodiments, anti-TREM2 antibodies of the present disclosure bind essentially the same TREM2 epitope bound by antibody AL2p-62.

[0152] In some embodiments, anti-TREM2 antibodies of the present disclosure compete with one or more antibodies selected from 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, and any combination thereof for binding to TREM2. In some embodiments, anti-TREM2 antibodies of the present disclosure compete with antibody AL2p-31 for binding to TREM2 for binding to TREM2. In some embodiments, anti-TREM2 antibodies of the present disclosure compete with antibody AL2p-37 for binding to TREM2. In some embodiments, anti-TREM2 antibodies of the present disclosure compete with antibody AL2p-47 for binding to TREM2. In some embodiments, anti-TREM2 antibodies of the present disclosure compete with antibody AL2p-58 for binding to TREM2. In some embodiments, anti-TREM2 antibodies of the present disclosure compete with antibody AL2p-60 for binding to TREM2. In some embodiments, anti-TREM2 antibodies of the present disclosure compete with antibody AL2p-61 for binding to TREM2. In some embodiments, anti-TREM2 antibodies of the present disclosure compete with antibody AL2p-62 for binding to TREM2.

[0153] In an exemplary competition assay, immobilized TREM2 or cells expressing TREM2 on the cell surface are incubated in a solution comprising a first labeled antibody that binds to TREM2 (*e.g.*, human or non-human primate) and a second unlabeled antibody that is being tested for its ability to compete with the first antibody for binding to TREM2. The second antibody may be present in a hybridoma supernatant. As a control, immobilized TREM2 or cells expressing TREM2 is incubated in a solution comprising the first labeled antibody but not the second unlabeled antibody. After incubation under conditions permissive for binding of the first antibody to TREM2, excess unbound antibody is removed, and the amount of label associated with immobilized TREM2 or cells expressing TREM2 is measured. If the amount of label associated with immobilized TREM2 or cells expressing TREM2 is substantially reduced in the test sample relative to the control sample, then that indicates that the second antibody is competing with the first antibody for binding to TREM2. *See*, Harlow and Lane (1988) *Antibodies: A Laboratory Manual* ch.14 (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY).

Anti-TREM2 antibody light chain and heavy chain variable regions

[0154] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise (a) a heavy chain variable region comprising at least one, two, or three HVRs selected from HVR-H1, HVR-H2, and HVR-H3 of any one of the antibodies listed in **Tables 2A-2C**, or selected from 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, and any combination thereof; and/or (b) a light chain variable region comprising at least one, two, or three HVRs selected from HVR-H1, HVR-H2, and HVR-H3 of any one of the antibodies listed in **Tables 3A-3C**, or selected from 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, and any combination thereof. In some embodiments, the HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2, and HVR-L3 comprise EU or Kabat HVR, Chothia HVR, or Contact HVR sequences as shown in **Tables 2A-2C, 3A-3C, 6, and 7**, or from an antibody selected from 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, and any combination thereof.

[0155] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise 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: $YAFX_1X_2X_3WMN$, wherein X_1 is S or W, X_2 is S, L, or R, and X_3 is S, D, H, Q, or E (SEQ ID NO: 121); an HVR-H2 comprising the sequence according to Formula II: $RIYPGX_1GX_2TNYAX_3KX_4X_5G$, wherein X_1 is D, G, E, Q, or V, X_2 is D or Q, X_3 is Q, R, H, W, Y, or G, X_4 is F, R, or W, and X_5 is Q, R, K, or H (SEQ ID NO: 122); and an HVR-H3 comprising the sequence according to Formula III: $ARLLRNX_1PGX_2SYAX_3DY$, wherein X_1 is Q or K, X_2 is E, S, or A, and X_3 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).

[0156] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise 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: $RX_1SX_2SLX_3HSNX_4YTYLH$, wherein X_1 is S or T, X_2 is Q, R, or S, X_3 is V or I, and X_4 is G, R,

W, Q, or A (SEQ ID NO: 127) an HVR-L2 comprising the sequence according to Formula V: KVSNRX$_1$S, wherein X$_1$ 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).

[0157] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise 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, wherein X$_1$ is S or W, X$_2$ is S, L, or R, and X$_3$ is S, D, H, Q, or E; an HVR-H2 comprising the sequence according to Formula II, wherein X$_1$ is D, G, E, Q, or V, X$_2$ is D or Q, X$_3$ is Q, R, H, W, Y, or G, X$_4$ is F, R, or W, and X$_5$ is Q, R, K, or H; and an HVR-H3 comprising the sequence according to Formula III, wherein X$_1$ is Q or K, X$_2$ is E, S, or A, and X$_3$ is M or H, and the light chain variable region comprises: an HVR-L1 comprising the sequence according to Formula IV, wherein X$_1$ is S or T, X$_2$ is Q, R, or S, X$_3$ is V or I, and X$_4$ is G, R, W, Q, or A; an HVR-L2 comprising the sequence according to Formula V, wherein X$_1$ is F, R, V, or K; 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).

[0158] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises one or more of: (a) an HVR-H1 comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to an HVR-H1 amino acid sequence 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; (b) an HVR-H2 comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least

92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to an HVR-H2 amino acid sequence 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; and (c) an HVR-H3 comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to an HVR-H3 amino acid sequence 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; and/or wherein the light chain variable domain comprises one or more of: (a) an HVR-L1 comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to an HVR-L1 amino acid sequence 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; (b) an HVR-L2 comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to an HVR-L1 amino acid sequence 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; and (c) an HVR-L3 comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least

89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to an HVR-L3 amino acid sequence 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.

[0159] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YAFSSQWMN (SEQ ID NO: 132), an HVR-H2 comprising the amino acid sequence RIYPGGGDTNYARKFQG (SEQ ID NO: 133), an HVR-H3 comprising the amino acid sequence ARLLRNQPGESYAMDY (SEQ ID NO: 126), and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLVHSNGYTYLH (SEQ ID NO: 130), an HVR-L2 comprising the amino acid sequence KVSNRRS (SEQ ID NO: 134), and an HVR-L3 comprising the amino acid sequence SQSTRVPYT (SEQ ID NO: 129). In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YAFSSQWMN (SEQ ID NO: 132), an HVR-H2 comprising the amino acid sequence RIYPGGGDTNYAGKFQG (SEQ ID NO: 135), an HVR-H3 comprising the amino acid sequence ARLLRNQPGESYAMDY (SEQ ID NO: 126), and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLVHSNGYTYLH (SEQ ID NO: 130), an HVR-L2 comprising the amino acid sequence KVSNRFS (SEQ ID NO: 131), and an HVR-L3 comprising the amino acid sequence SQSTRVPYT (SEQ ID NO: 129). In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YAFSSDWMN (SEQ ID NO: 136), an HVR-H2 comprising the amino acid sequence RIYPGEGDTNYARKFHG (SEQ ID NO: 137), an HVR-H3 comprising the amino acid sequence ARLLRNKPGESYAMDY (SEQ ID NO: 138), and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RTSQSLVHSNAYTYLH (SEQ ID NO: 139), an HVR-L2 comprising the amino acid sequence KVSNRVS (SEQ ID NO: 140), and an HVR-L3 comprising the amino acid sequence SQSTRVPYT (SEQ ID NO: 129). In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YAFSSQWMN (SEQ ID NO: 132), an HVR-H2 comprising the amino acid sequence RIYPGEGDTNYARKFQG (SEQ ID NO: 141), an HVR-H3 comprising the amino acid sequence ARLLRNQPGESYAMDY (SEQ ID NO:

126), and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLVHSNQYTYLH (SEQ ID NO: 142), an HVR-L2 comprising the amino acid sequence KVSNRRS (SEQ ID NO: 134), and an HVR-L3 comprising the amino acid sequence SQSTRVPYT (SEQ ID NO: 129). In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YAFSSQWMN (SEQ ID NO: 132), an HVR-H2 comprising the amino acid sequence RIYPGEGDTNYAGKFQG (SEQ ID NO: 143), an HVR-H3 comprising the amino acid sequence ARLLRNQPGESYAMDY (SEQ ID NO: 126), and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLVHSNQYTYLH (SEQ ID NO: 142), an HVR-L2 comprising the amino acid sequence KVSNRFS (SEQ ID NO: 131), and an HVR-L3 comprising the amino acid sequence SQSTRVPYT (SEQ ID NO: 129). In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YAFSSQWMN (SEQ ID NO: 132), an HVR-H2 comprising the amino acid sequence RIYPGGGDTNYAGKFQG (SEQ ID NO: 135), an HVR-H3 comprising the amino acid sequence ARLLRNQPGESYAMDY (SEQ ID NO: 126), and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLVHSNRYTYLH (SEQ ID NO: 144), an HVR-L2 comprising the amino acid sequence KVSNRFS (SEQ ID NO: 131), and an HVR-L3 comprising the amino acid sequence SQSTRVPYT (SEQ ID NO: 129). In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YAFSSQWMN (SEQ ID NO: 132), an HVR-H2 comprising the amino acid sequence RIYPGGGDTNYARKFQG (SEQ ID NO: 133), an HVR-H3 comprising the amino acid sequence ARLLRNQPGESYAMDY (SEQ ID NO: 126), and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLVHSNRYTYLH (SEQ ID NO: 144), an HVR-L2 comprising the amino acid sequence KVSNRRS (SEQ ID NO: 134), and an HVR-L3 comprising the amino acid sequence SQSTRVPYT (SEQ ID NO: 129). In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable region and a light chain variable region, wherein 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 L 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.

[0160] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable region of any one of the antibodies listed in **Table 6A**, or selected from 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; and/or a light chain variable region of any one of the antibodies listed in **Table 7A**, or selected from 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 embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable region comprising an amino acid sequence selected from any of SEQ ID NOs: 27-71 and 91; and/or a light chain variable domain comprising an amino acid sequence selected from any of SEQ ID NOs: 92-113 and 118. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable region comprising an amino acid sequence selected from any of SEQ ID NOs: 27, 56 and 72-90; and/or a light chain variable domain comprising an amino acid sequence selected from any of SEQ ID NOs: 92, 104, and 114-117.

[0161] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-2 or to the amino acid sequence of SEQ ID NO: 28; and/or the light chain

variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-2 or to the amino acid sequence of SEQ ID NO: 92. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-2 or to the amino acid sequence of SEQ ID NO: 28, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-2. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-2 or to the amino acid sequence of SEQ ID NO: 92, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-2. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-2 or to the amino acid sequence of SEQ ID NO: 28 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-2 or the amino acid sequence of SEQ ID NO: 28. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-2 or the amino acid sequence of SEQ ID NO: 28. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-2 or of SEQ ID NO: 28, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-2, (b) the HVR-H2 amino acid sequence of antibody AL2p-2, and (c) the HVR-H3 amino acid sequence of antibody AL2p-2. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least

93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-2 or to the amino acid sequence of SEQ ID NO: 92 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-2 or the amino acid sequence of SEQ ID NO: 92. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-2 or the amino acid sequence of SEQ ID NO: 92. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-2 or of SEQ ID NO: 92, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-2, (b) the HVR-L2 amino acid sequence of antibody AL2p-2, and (c) the HVR-L3 amino acid sequence of antibody AL2p-2.

[0162] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-3 or to the amino acid sequence of SEQ ID NO: 29; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-3 or to the amino acid sequence of SEQ ID NO: 92. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-3 or to the amino acid sequence of SEQ ID NO: 29, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-3. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-3 or to the amino

acid sequence of SEQ ID NO: 92, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-3. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-3 or to the amino acid sequence of SEQ ID NO: 29 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-3 or the amino acid sequence of SEQ ID NO: 29. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-3 or the amino acid sequence of SEQ ID NO: 29. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-3 or of SEQ ID NO: 29, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-3, (b) the HVR-H2 amino acid sequence of antibody AL2p-3, and (c) the HVR-H3 amino acid sequence of antibody AL2p-3. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-3 or to the amino acid sequence of SEQ ID NO: 92 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-3 or the amino acid sequence of SEQ ID NO: 92. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-3 or the amino acid sequence of SEQ ID NO: 92. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-3 or of SEQ ID NO: 92, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1

amino acid sequence of antibody AL2p-3, (b) the HVR-L2 amino acid sequence of antibody AL2p-3, and (c) the HVR-L3 amino acid sequence of antibody AL2p-3.

[0163] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-4 or to the amino acid sequence of SEQ ID NO: 30; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-4 or to the amino acid sequence of SEQ ID NO: 92. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-4 or to the amino acid sequence of SEQ ID NO: 30, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-4. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-4 or to the amino acid sequence of SEQ ID NO: 92, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-4. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-4 or to the amino acid sequence of SEQ ID NO: 30 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-4 or the amino acid sequence of SEQ ID NO: 30. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-4 or the amino acid sequence of SEQ ID NO: 30. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in

the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-4 or of SEQ ID NO: 30, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-4, (b) the HVR-H2 amino acid sequence of antibody AL2p-4, and (c) the HVR-H3 amino acid sequence of antibody AL2p-4. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-4 or to the amino acid sequence of SEQ ID NO: 92 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-4 or the amino acid sequence of SEQ ID NO: 92. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-4 or the amino acid sequence of SEQ ID NO: 92. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-4 or of SEQ ID NO: 92, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-4, (b) the HVR-L2 amino acid sequence of antibody AL2p-4, and (c) the HVR-L3 amino acid sequence of antibody AL2p-4.

[0164] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-7 or to the amino acid sequence of SEQ ID NO: 31; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-7 or to the amino acid sequence of SEQ ID NO: 95. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least

95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-7 or to the amino acid sequence of SEQ ID NO: 31, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-7. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-7 or to the amino acid sequence of SEQ ID NO: 95, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-7. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-7 or to the amino acid sequence of SEQ ID NO: 31 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-7 or the amino acid sequence of SEQ ID NO: 31. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-7 or the amino acid sequence of SEQ ID NO: 31. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-7 or of SEQ ID NO: 31, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-7, (b) the HVR-H2 amino acid sequence of antibody AL2p-7, and (c) the HVR-H3 amino acid sequence of antibody AL2p-7. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-7 or to the amino acid sequence of SEQ ID NO: 95 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-7 or the amino acid sequence of SEQ ID NO: 95. In certain

embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-7 or the amino acid sequence of SEQ ID NO: 95. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-7 or of SEQ ID NO: 95, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-7, (b) the HVR-L2 amino acid sequence of antibody AL2p-7, and (c) the HVR-L3 amino acid sequence of antibody AL2p-7.

[0165] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-8 or to the amino acid sequence of SEQ ID NO: 32; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-8 or to the amino acid sequence of SEQ ID NO: 95. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-8 or to the amino acid sequence of SEQ ID NO: 32, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-8. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-8 or to the amino acid sequence of SEQ ID NO: 95, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-8. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-8 or to the amino acid sequence of SEQ ID NO: 32 and contains substitutions (*e.g.*, conservative substitutions,

insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-8 or the amino acid sequence of SEQ ID NO: 32. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-8 or the amino acid sequence of SEQ ID NO: 32. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-8 or of SEQ ID NO: 32, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-8, (b) the HVR-H2 amino acid sequence of antibody AL2p-8, and (c) the HVR-H3 amino acid sequence of antibody AL2p-8. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-8 or to the amino acid sequence of SEQ ID NO: 95 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-8 or the amino acid sequence of SEQ ID NO: 95. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-8 or the amino acid sequence of SEQ ID NO: 95. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-8 or of SEQ ID NO: 95, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-8, (b) the HVR-L2 amino acid sequence of antibody AL2p-8, and (c) the HVR-L3 amino acid sequence of antibody AL2p-8.

[0166] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-9 or to the amino acid sequence of SEQ ID NO: 33; and/or the light chain

variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-9 or to the amino acid sequence of SEQ ID NO: 96. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-9 or to the amino acid sequence of SEQ ID NO: 33, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-9. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-9 or to the amino acid sequence of SEQ ID NO: 96, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-9. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-9 or to the amino acid sequence of SEQ ID NO: 33 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-9 or the amino acid sequence of SEQ ID NO: 33. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-9 or the amino acid sequence of SEQ ID NO: 33. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-9 or of SEQ ID NO: 33, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-9, (b) the HVR-H2 amino acid sequence of antibody AL2p-9, and (c) the HVR-H3 amino acid sequence of antibody AL2p-9. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least

93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-9 or to the amino acid sequence of SEQ ID NO: 96 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-9 or the amino acid sequence of SEQ ID NO: 96. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-9 or the amino acid sequence of SEQ ID NO: 96. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-9 or of SEQ ID NO: 96, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-9, (b) the HVR-L2 amino acid sequence of antibody AL2p-9, and (c) the HVR-L3 amino acid sequence of antibody AL2p-9.

[0167] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-10 or to the amino acid sequence of SEQ ID NO: 34; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-10 or to the amino acid sequence of SEQ ID NO: 97. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-10 or to the amino acid sequence of SEQ ID NO: 34, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-10. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-10 or to the

amino acid sequence of SEQ ID NO: 97, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-10. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-10 or to the amino acid sequence of SEQ ID NO: 34 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-10 or the amino acid sequence of SEQ ID NO: 34. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-10 or the amino acid sequence of SEQ ID NO: 34. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-10 or of SEQ ID NO: 34, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-10, (b) the HVR-H2 amino acid sequence of antibody AL2p-10, and (c) the HVR-H3 amino acid sequence of antibody AL2p-10. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-10 or to the amino acid sequence of SEQ ID NO: 97 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-10 or the amino acid sequence of SEQ ID NO: 97. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-10 or the amino acid sequence of SEQ ID NO: 97. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-10 or of SEQ ID NO: 97, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1

amino acid sequence of antibody AL2p-10, (b) the HVR-L2 amino acid sequence of antibody AL2p-10, and (c) the HVR-L3 amino acid sequence of antibody AL2p-10.

[0168] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-11 or to the amino acid sequence of SEQ ID NO: 35; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-11 or to the amino acid sequence of SEQ ID NO: 98. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-11 or to the amino acid sequence of SEQ ID NO: 35, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-11. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-11 or to the amino acid sequence of SEQ ID NO: 98, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-11. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-11 or to the amino acid sequence of SEQ ID NO: 35 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-11 or the amino acid sequence of SEQ ID NO: 35. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-11 or the amino acid sequence of SEQ ID NO: 35. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the

HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-11 or of SEQ ID NO: 35, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-11, (b) the HVR-H2 amino acid sequence of antibody AL2p-11, and (c) the HVR-H3 amino acid sequence of antibody AL2p-11. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-11 or to the amino acid sequence of SEQ ID NO: 98 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-11 or the amino acid sequence of SEQ ID NO: 98. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-11 or the amino acid sequence of SEQ ID NO: 98. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-11 or of SEQ ID NO: 98, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-11, (b) the HVR-L2 amino acid sequence of antibody AL2p-11, and (c) the HVR-L3 amino acid sequence of antibody AL2p-11.

[0169] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-12 or to the amino acid sequence of SEQ ID NO: 36; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-12 or to the amino acid sequence of SEQ ID NO: 97. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at

least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-12 or to the amino acid sequence of SEQ ID NO: 36, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-12. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-12 or to the amino acid sequence of SEQ ID NO: 97, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-12. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-12 or to the amino acid sequence of SEQ ID NO: 36 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-12 or the amino acid sequence of SEQ ID NO: 36. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-12 or the amino acid sequence of SEQ ID NO: 36. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-12 or of SEQ ID NO: 36, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-12, (b) the HVR-H2 amino acid sequence of antibody AL2p-12, and (c) the HVR-H3 amino acid sequence of antibody AL2p-12. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-12 or to the amino acid sequence of SEQ ID NO: 97 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-12 or the amino acid sequence of SEQ ID NO: 97. In certain

embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-12 or the amino acid sequence of SEQ ID NO: 97. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-12 or of SEQ ID NO: 97, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-12, (b) the HVR-L2 amino acid sequence of antibody AL2p-12, and (c) the HVR-L3 amino acid sequence of antibody AL2p-12.

[0170] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-13 or to the amino acid sequence of SEQ ID NO: 37; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-13 or to the amino acid sequence of SEQ ID NO: 95. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-13 or to the amino acid sequence of SEQ ID NO: 37, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-13. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-13 or to the amino acid sequence of SEQ ID NO: 95, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-13. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-13 or to the amino acid sequence of SEQ ID NO: 37 and contains substitutions (*e.g.*, conservative substitutions,

insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-13 or the amino acid sequence of SEQ ID NO: 37. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-13 or the amino acid sequence of SEQ ID NO: 37. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-13 or of SEQ ID NO: 37, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-13, (b) the HVR-H2 amino acid sequence of antibody AL2p-13, and (c) the HVR-H3 amino acid sequence of antibody AL2p-13. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-13 or to the amino acid sequence of SEQ ID NO: 95 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-13 or the amino acid sequence of SEQ ID NO: 95. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-13 or the amino acid sequence of SEQ ID NO: 95. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-13 or of SEQ ID NO: 95, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-13, (b) the HVR-L2 amino acid sequence of antibody AL2p-13, and (c) the HVR-L3 amino acid sequence of antibody AL2p-13.

[0171] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-14 or to the amino acid sequence of SEQ ID NO: 38; and/or the light

chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-14 or to the amino acid sequence of SEQ ID NO: 99. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-14 or to the amino acid sequence of SEQ ID NO: 38, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-14. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-14 or to the amino acid sequence of SEQ ID NO: 99, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-14. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-14 or to the amino acid sequence of SEQ ID NO: 38 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-14 or the amino acid sequence of SEQ ID NO: 38. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-14 or the amino acid sequence of SEQ ID NO: 38. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-14 or of SEQ ID NO: 38, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-14, (b) the HVR-H2 amino acid sequence of antibody AL2p-14, and (c) the HVR-H3 amino acid sequence of antibody AL2p-14. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%,

at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-14 or to the amino acid sequence of SEQ ID NO: 99 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-14 or the amino acid sequence of SEQ ID NO: 99. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-14 or the amino acid sequence of SEQ ID NO: 99. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-14 or of SEQ ID NO: 99, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-14, (b) the HVR-L2 amino acid sequence of antibody AL2p-14, and (c) the HVR-L3 amino acid sequence of antibody AL2p-14.

[0172] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-15 or to the amino acid sequence of SEQ ID NO: 38; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-15 or to the amino acid sequence of SEQ ID NO: 100. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-15 or to the amino acid sequence of SEQ ID NO: 38, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-15. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-15 or to the

amino acid sequence of SEQ ID NO: 100, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-15. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-15 or to the amino acid sequence of SEQ ID NO: 38 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-15 or the amino acid sequence of SEQ ID NO: 38. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-15 or the amino acid sequence of SEQ ID NO: 38. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-15 or of SEQ ID NO: 38, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-15, (b) the HVR-H2 amino acid sequence of antibody AL2p-15, and (c) the HVR-H3 amino acid sequence of antibody AL2p-15. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-15 or to the amino acid sequence of SEQ ID NO: 100 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-15 or the amino acid sequence of SEQ ID NO: 100. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-15 or the amino acid sequence of SEQ ID NO: 100. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-15 or of SEQ ID NO: 100, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1

amino acid sequence of antibody AL2p-15, (b) the HVR-L2 amino acid sequence of antibody AL2p-15, and (c) the HVR-L3 amino acid sequence of antibody AL2p-15.

[0173] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-16 or to the amino acid sequence of SEQ ID NO: 39; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-16 or to the amino acid sequence of SEQ ID NO: 96. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-16 or to the amino acid sequence of SEQ ID NO: 39, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-16. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-16 or to the amino acid sequence of SEQ ID NO: 96, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-16. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-16 or to the amino acid sequence of SEQ ID NO: 39 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-16 or the amino acid sequence of SEQ ID NO: 39. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-16 or the amino acid sequence of SEQ ID NO: 39. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the

HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-16 or of SEQ ID NO: 39, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-16, (b) the HVR-H2 amino acid sequence of antibody AL2p-16, and (c) the HVR-H3 amino acid sequence of antibody AL2p-16. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-16 or to the amino acid sequence of SEQ ID NO: 96 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-16 or the amino acid sequence of SEQ ID NO: 96. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-16 or the amino acid sequence of SEQ ID NO: 96. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-16 or of SEQ ID NO: 96, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-16, (b) the HVR-L2 amino acid sequence of antibody AL2p-16, and (c) the HVR-L3 amino acid sequence of antibody AL2p-16.

[0174] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-17 or to the amino acid sequence of SEQ ID NO: 40; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-17 or to the amino acid sequence of SEQ ID NO: 98. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at

least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-17 or to the amino acid sequence of SEQ ID NO: 40, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-17. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-17 or to the amino acid sequence of SEQ ID NO: 98, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-17. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-17 or to the amino acid sequence of SEQ ID NO: 40 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-17 or the amino acid sequence of SEQ ID NO: 40. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-17 or the amino acid sequence of SEQ ID NO: 40. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-17 or of SEQ ID NO: 40, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-17, (b) the HVR-H2 amino acid sequence of antibody AL2p-17, and (c) the HVR-H3 amino acid sequence of antibody AL2p-17. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-17 or to the amino acid sequence of SEQ ID NO: 98 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-17 or the amino acid sequence of SEQ ID NO: 98. In certain

embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-17 or the amino acid sequence of SEQ ID NO: 98. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-17 or of SEQ ID NO: 98, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-17, (b) the HVR-L2 amino acid sequence of antibody AL2p-17, and (c) the HVR-L3 amino acid sequence of antibody AL2p-17.

[0175] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-18 or to the amino acid sequence of SEQ ID NO: 41; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-18 or to the amino acid sequence of SEQ ID NO: 96. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-18 or to the amino acid sequence of SEQ ID NO: 41, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-18. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-18 or to the amino acid sequence of SEQ ID NO: 96, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-18. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-18 or to the amino acid sequence of SEQ ID NO: 41 and contains substitutions (*e.g.*, conservative substitutions,

insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-18 or the amino acid sequence of SEQ ID NO: 41. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-18 or the amino acid sequence of SEQ ID NO: 41. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-18 or of SEQ ID NO: 41, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-18, (b) the HVR-H2 amino acid sequence of antibody AL2p-18, and (c) the HVR-H3 amino acid sequence of antibody AL2p-18. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-18 or to the amino acid sequence of SEQ ID NO: 96 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-18 or the amino acid sequence of SEQ ID NO: 96. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-18 or the amino acid sequence of SEQ ID NO: 96. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-18 or of SEQ ID NO: 96, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-18, (b) the HVR-L2 amino acid sequence of antibody AL2p-18, and (c) the HVR-L3 amino acid sequence of antibody AL2p-18.

[0176] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-19 or to the amino acid sequence of SEQ ID NO: 42; and/or the light

chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-19 or to the amino acid sequence of SEQ ID NO: 98. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-19 or to the amino acid sequence of SEQ ID NO: 42, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-19. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-19 or to the amino acid sequence of SEQ ID NO: 98, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-19. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-19 or to the amino acid sequence of SEQ ID NO: 42 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-19 or the amino acid sequence of SEQ ID NO: 42. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-19 or the amino acid sequence of SEQ ID NO: 42. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-19 or of SEQ ID NO: 42, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-19, (b) the HVR-H2 amino acid sequence of antibody AL2p-19, and (c) the HVR-H3 amino acid sequence of antibody AL2p-19. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%,

at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-19 or to the amino acid sequence of SEQ ID NO: 98 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-19 or the amino acid sequence of SEQ ID NO: 98. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-19 or the amino acid sequence of SEQ ID NO: 98. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-19 or of SEQ ID NO: 98, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-19, (b) the HVR-L2 amino acid sequence of antibody AL2p-19, and (c) the HVR-L3 amino acid sequence of antibody AL2p-19.

[0177] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-20 or to the amino acid sequence of SEQ ID NO: 42; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-20 or to the amino acid sequence of SEQ ID NO: 96. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-20 or to the amino acid sequence of SEQ ID NO: 42, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-20. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-20 or to the

amino acid sequence of SEQ ID NO: 96, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-20. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-20 or to the amino acid sequence of SEQ ID NO: 42 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-20 or the amino acid sequence of SEQ ID NO: 42. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-20 or the amino acid sequence of SEQ ID NO: 42. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-20 or of SEQ ID NO: 42, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-20, (b) the HVR-H2 amino acid sequence of antibody AL2p-20, and (c) the HVR-H3 amino acid sequence of antibody AL2p-20. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-20 or to the amino acid sequence of SEQ ID NO: 96 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-20 or the amino acid sequence of SEQ ID NO: 96. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-20 or the amino acid sequence of SEQ ID NO: 96. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-20 or of SEQ ID NO: 96, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1

amino acid sequence of antibody AL2p-20, (b) the HVR-L2 amino acid sequence of antibody AL2p-20, and (c) the HVR-L3 amino acid sequence of antibody AL2p-20.

[0178] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-21 or to the amino acid sequence of SEQ ID NO: 43; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-21 or to the amino acid sequence of SEQ ID NO: 100. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-21 or to the amino acid sequence of SEQ ID NO: 43, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-21. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-21 or to the amino acid sequence of SEQ ID NO: 100, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-21. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-21 or to the amino acid sequence of SEQ ID NO: 43 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-21 or the amino acid sequence of SEQ ID NO: 43. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-21 or the amino acid sequence of SEQ ID NO: 43. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the

HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-21 or of SEQ ID NO: 43, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-21, (b) the HVR-H2 amino acid sequence of antibody AL2p-21, and (c) the HVR-H3 amino acid sequence of antibody AL2p-21. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-21 or to the amino acid sequence of SEQ ID NO: 100 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-21 or the amino acid sequence of SEQ ID NO: 100. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-21 or the amino acid sequence of SEQ ID NO: 100. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-21 or of SEQ ID NO: 100, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-21, (b) the HVR-L2 amino acid sequence of antibody AL2p-21, and (c) the HVR-L3 amino acid sequence of antibody AL2p-21.

[0179] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-22 or to the amino acid sequence of SEQ ID NO: 44; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-22 or to the amino acid sequence of SEQ ID NO: 101. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at

least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-22 or to the amino acid sequence of SEQ ID NO: 44, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-22. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-22 or to the amino acid sequence of SEQ ID NO: 101, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-22. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-22 or to the amino acid sequence of SEQ ID NO: 44 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-22 or the amino acid sequence of SEQ ID NO: 44. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-22 or the amino acid sequence of SEQ ID NO: 44. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-22 or of SEQ ID NO: 44, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-22, (b) the HVR-H2 amino acid sequence of antibody AL2p-22, and (c) the HVR-H3 amino acid sequence of antibody AL2p-22. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-22 or to the amino acid sequence of SEQ ID NO: 101 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-22 or the amino acid sequence of SEQ ID NO: 101. In certain

embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-22 or the amino acid sequence of SEQ ID NO: 101. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-22 or of SEQ ID NO: 101, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-22, (b) the HVR-L2 amino acid sequence of antibody AL2p-22, and (c) the HVR-L3 amino acid sequence of antibody AL2p-22.

[0180] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-23 or to the amino acid sequence of SEQ ID NO: 45; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-23 or to the amino acid sequence of SEQ ID NO: 96. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-23 or to the amino acid sequence of SEQ ID NO: 45, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-23. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-23 or to the amino acid sequence of SEQ ID NO: 96, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-23. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-23 or to the amino acid sequence of SEQ ID NO: 45 and contains substitutions (*e.g.*, conservative substitutions,

insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-23 or the amino acid sequence of SEQ ID NO: 45. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-23 or the amino acid sequence of SEQ ID NO: 45. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-23 or of SEQ ID NO: 45, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-23, (b) the HVR-H2 amino acid sequence of antibody AL2p-23, and (c) the HVR-H3 amino acid sequence of antibody AL2p-23. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-23 or to the amino acid sequence of SEQ ID NO: 96 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-23 or the amino acid sequence of SEQ ID NO: 96. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-23 or the amino acid sequence of SEQ ID NO: 96. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-23 or of SEQ ID NO: 96, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-23, (b) the HVR-L2 amino acid sequence of antibody AL2p-23, and (c) the HVR-L3 amino acid sequence of antibody AL2p-23.

[0181] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-24 or to the amino acid sequence of SEQ ID NO: 46; and/or the light

chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-24 or to the amino acid sequence of SEQ ID NO: 99. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-24 or to the amino acid sequence of SEQ ID NO: 46, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-24. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-24 or to the amino acid sequence of SEQ ID NO: 99, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-24. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-24 or to the amino acid sequence of SEQ ID NO: 46 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-24 or the amino acid sequence of SEQ ID NO: 46. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-24 or the amino acid sequence of SEQ ID NO: 46. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-24 or of SEQ ID NO: 46, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-24, (b) the HVR-H2 amino acid sequence of antibody AL2p-24, and (c) the HVR-H3 amino acid sequence of antibody AL2p-24. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%,

at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-24 or to the amino acid sequence of SEQ ID NO: 99 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-24 or the amino acid sequence of SEQ ID NO: 99. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-24 or the amino acid sequence of SEQ ID NO: 99. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-24 or of SEQ ID NO: 99, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-24, (b) the HVR-L2 amino acid sequence of antibody AL2p-24, and (c) the HVR-L3 amino acid sequence of antibody AL2p-24.

[0182] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-25 or to the amino acid sequence of SEQ ID NO: 47; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-25 or to the amino acid sequence of SEQ ID NO: 96. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-25 or to the amino acid sequence of SEQ ID NO: 47, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-25. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-25 or to the

amino acid sequence of SEQ ID NO: 96, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-25. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-25 or to the amino acid sequence of SEQ ID NO: 47 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-25 or the amino acid sequence of SEQ ID NO: 47. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-25 or the amino acid sequence of SEQ ID NO: 47. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-25 or of SEQ ID NO: 47, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-25, (b) the HVR-H2 amino acid sequence of antibody AL2p-25, and (c) the HVR-H3 amino acid sequence of antibody AL2p-25. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-25 or to the amino acid sequence of SEQ ID NO: 96 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-25 or the amino acid sequence of SEQ ID NO: 96. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-25 or the amino acid sequence of SEQ ID NO: 96. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-25 or of SEQ ID NO: 96, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1

amino acid sequence of antibody AL2p-25, (b) the HVR-L2 amino acid sequence of antibody AL2p-25, and (c) the HVR-L3 amino acid sequence of antibody AL2p-25.

[0183] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-26 or to the amino acid sequence of SEQ ID NO: 48; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-26 or to the amino acid sequence of SEQ ID NO: 95. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-26 or to the amino acid sequence of SEQ ID NO: 48, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-26. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-26 or to the amino acid sequence of SEQ ID NO: 95, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-26. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-26 or to the amino acid sequence of SEQ ID NO: 48 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-26 or the amino acid sequence of SEQ ID NO: 48. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-26 or the amino acid sequence of SEQ ID NO: 48. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the

HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-26 or of SEQ ID NO: 48, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-26, (b) the HVR-H2 amino acid sequence of antibody AL2p-26, and (c) the HVR-H3 amino acid sequence of antibody AL2p-26. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-26 or to the amino acid sequence of SEQ ID NO: 95 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-26 or the amino acid sequence of SEQ ID NO: 95. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-26 or the amino acid sequence of SEQ ID NO: 95. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-26 or of SEQ ID NO: 95, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-26, (b) the HVR-L2 amino acid sequence of antibody AL2p-26, and (c) the HVR-L3 amino acid sequence of antibody AL2p-26.

[0184] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-27 or to the amino acid sequence of SEQ ID NO: 49; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-27 or to the amino acid sequence of SEQ ID NO: 102. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at

least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-27 or to the amino acid sequence of SEQ ID NO: 49, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-27. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-27 or to the amino acid sequence of SEQ ID NO: 102, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-27. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-27 or to the amino acid sequence of SEQ ID NO: 49 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-27 or the amino acid sequence of SEQ ID NO: 49. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-27 or the amino acid sequence of SEQ ID NO: 49. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-27 or of SEQ ID NO: 49, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-27, (b) the HVR-H2 amino acid sequence of antibody AL2p-27, and (c) the HVR-H3 amino acid sequence of antibody AL2p-27. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-27 or to the amino acid sequence of SEQ ID NO: 102 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-27 or the amino acid sequence of SEQ ID NO: 102. In certain

embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-27 or the amino acid sequence of SEQ ID NO: 102. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-27 or of SEQ ID NO: 102, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-27, (b) the HVR-L2 amino acid sequence of antibody AL2p-27, and (c) the HVR-L3 amino acid sequence of antibody AL2p-27.

[0185] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-28 or to the amino acid sequence of SEQ ID NO: 50; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-28 or to the amino acid sequence of SEQ ID NO: 96. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-28 or to the amino acid sequence of SEQ ID NO: 50, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-28. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-28 or to the amino acid sequence of SEQ ID NO: 96, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-28. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-28 or to the amino acid sequence of SEQ ID NO: 50 and contains substitutions (*e.g.*, conservative substitutions,

insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-28 or the amino acid sequence of SEQ ID NO: 50. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-28 or the amino acid sequence of SEQ ID NO: 50. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-28 or of SEQ ID NO: 50, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-28, (b) the HVR-H2 amino acid sequence of antibody AL2p-28, and (c) the HVR-H3 amino acid sequence of antibody AL2p-28. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-28 or to the amino acid sequence of SEQ ID NO: 96 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-28 or the amino acid sequence of SEQ ID NO: 96. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-28 or the amino acid sequence of SEQ ID NO: 96. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-28 or of SEQ ID NO: 96, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-28, (b) the HVR-L2 amino acid sequence of antibody AL2p-28, and (c) the HVR-L3 amino acid sequence of antibody AL2p-28.

[0186] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-29 or to the amino acid sequence of SEQ ID NO: 51; and/or the light

chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-29 or to the amino acid sequence of SEQ ID NO: 99. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-29 or to the amino acid sequence of SEQ ID NO: 51, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-29. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-29 or to the amino acid sequence of SEQ ID NO: 99, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-29. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-29 or to the amino acid sequence of SEQ ID NO: 51 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-29 or the amino acid sequence of SEQ ID NO: 51. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-29 or the amino acid sequence of SEQ ID NO: 51. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-29 or of SEQ ID NO: 51, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-29, (b) the HVR-H2 amino acid sequence of antibody AL2p-29, and (c) the HVR-H3 amino acid sequence of antibody AL2p-29. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%,

at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-29 or to the amino acid sequence of SEQ ID NO: 99 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-29 or the amino acid sequence of SEQ ID NO: 99. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-29 or the amino acid sequence of SEQ ID NO: 99. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-29 or of SEQ ID NO: 99, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-29, (b) the HVR-L2 amino acid sequence of antibody AL2p-29, and (c) the HVR-L3 amino acid sequence of antibody AL2p-29.

[0187] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-30 or to the amino acid sequence of SEQ ID NO: 52; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-30 or to the amino acid sequence of SEQ ID NO: 100. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-30 or to the amino acid sequence of SEQ ID NO: 52, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-30. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-30 or to the

amino acid sequence of SEQ ID NO: 100, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-30. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-30 or to the amino acid sequence of SEQ ID NO: 52 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-30 or the amino acid sequence of SEQ ID NO: 52. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-30 or the amino acid sequence of SEQ ID NO: 52. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-30 or of SEQ ID NO: 52, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-30, (b) the HVR-H2 amino acid sequence of antibody AL2p-30, and (c) the HVR-H3 amino acid sequence of antibody AL2p-30. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-30 or to the amino acid sequence of SEQ ID NO: 100 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-30 or the amino acid sequence of SEQ ID NO: 100. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-30 or the amino acid sequence of SEQ ID NO: 100. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-30 or of SEQ ID NO: 100, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1

amino acid sequence of antibody AL2p-30, (b) the HVR-L2 amino acid sequence of antibody AL2p-30, and (c) the HVR-L3 amino acid sequence of antibody AL2p-30.

[0188] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-31 or to the amino acid sequence of SEQ ID NO: 53; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-31 or to the amino acid sequence of SEQ ID NO: 97. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-31 or to the amino acid sequence of SEQ ID NO: 53, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-31. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-31 or to the amino acid sequence of SEQ ID NO: 97, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-31. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-31 or to the amino acid sequence of SEQ ID NO: 53 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-31 or the amino acid sequence of SEQ ID NO: 53. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-31 or the amino acid sequence of SEQ ID NO: 53. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the

HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-31 or of SEQ ID NO: 53, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-31, (b) the HVR-H2 amino acid sequence of antibody AL2p-31, and (c) the HVR-H3 amino acid sequence of antibody AL2p-31. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-31 or to the amino acid sequence of SEQ ID NO: 97 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-31 or the amino acid sequence of SEQ ID NO: 97. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-31 or the amino acid sequence of SEQ ID NO: 97. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-31 or of SEQ ID NO: 97, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-31, (b) the HVR-L2 amino acid sequence of antibody AL2p-31, and (c) the HVR-L3 amino acid sequence of antibody AL2p-31.

[0189] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-32 or to the amino acid sequence of SEQ ID NO: 54; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-32 or to the amino acid sequence of SEQ ID NO: 97. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at

least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-32 or to the amino acid sequence of SEQ ID NO: 54, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-32. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-32 or to the amino acid sequence of SEQ ID NO: 97, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-32. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-32 or to the amino acid sequence of SEQ ID NO: 54 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-32 or the amino acid sequence of SEQ ID NO: 54. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-32 or the amino acid sequence of SEQ ID NO: 54. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-32 or of SEQ ID NO: 54, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-32, (b) the HVR-H2 amino acid sequence of antibody AL2p-32, and (c) the HVR-H3 amino acid sequence of antibody AL2p-32. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-32 or to the amino acid sequence of SEQ ID NO: 97 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-32 or the amino acid sequence of SEQ ID NO: 97. In certain

embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-32 or the amino acid sequence of SEQ ID NO: 97. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-32 or of SEQ ID NO: 97, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-32, (b) the HVR-L2 amino acid sequence of antibody AL2p-32, and (c) the HVR-L3 amino acid sequence of antibody AL2p-32.

[0190] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-33 or to the amino acid sequence of SEQ ID NO: 55; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-33 or to the amino acid sequence of SEQ ID NO: 103. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-33 or to the amino acid sequence of SEQ ID NO: 55, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-33. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-33 or to the amino acid sequence of SEQ ID NO: 103, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-33. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-33 or to the amino acid sequence of SEQ ID NO: 55 and contains substitutions (*e.g.*, conservative substitutions,

insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-33 or the amino acid sequence of SEQ ID NO: 55. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-33 or the amino acid sequence of SEQ ID NO: 55. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-33 or of SEQ ID NO: 55, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-33, (b) the HVR-H2 amino acid sequence of antibody AL2p-33, and (c) the HVR-H3 amino acid sequence of antibody AL2p-33. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-33 or to the amino acid sequence of SEQ ID NO: 103 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-33 or the amino acid sequence of SEQ ID NO: 103. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-33 or the amino acid sequence of SEQ ID NO: 103. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-33 or of SEQ ID NO: 103, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-33, (b) the HVR-L2 amino acid sequence of antibody AL2p-33, and (c) the HVR-L3 amino acid sequence of antibody AL2p-33.

[0191] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-35 or to the amino acid sequence of SEQ ID NO: 57; and/or the light

chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-35 or to the amino acid sequence of SEQ ID NO: 104. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-35 or to the amino acid sequence of SEQ ID NO: 57, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-35. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-35 or to the amino acid sequence of SEQ ID NO: 104, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-35. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-35 or to the amino acid sequence of SEQ ID NO: 57 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-35 or the amino acid sequence of SEQ ID NO: 57. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-35 or the amino acid sequence of SEQ ID NO: 57. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-35 or of SEQ ID NO: 57, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-35, (b) the HVR-H2 amino acid sequence of antibody AL2p-35, and (c) the HVR-H3 amino acid sequence of antibody AL2p-35. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%,

at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-35 or to the amino acid sequence of SEQ ID NO: 104 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-35 or the amino acid sequence of SEQ ID NO: 104. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-35 or the amino acid sequence of SEQ ID NO: 104. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-35 or of SEQ ID NO: 104, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-35, (b) the HVR-L2 amino acid sequence of antibody AL2p-35, and (c) the HVR-L3 amino acid sequence of antibody AL2p-35.

[0192] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-36 or to the amino acid sequence of SEQ ID NO: 58; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-36 or to the amino acid sequence of SEQ ID NO: 104. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-36 or to the amino acid sequence of SEQ ID NO: 58, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-36. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-36 or to the

amino acid sequence of SEQ ID NO: 104, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-36. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-36 or to the amino acid sequence of SEQ ID NO: 58 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-36 or the amino acid sequence of SEQ ID NO: 58. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-36 or the amino acid sequence of SEQ ID NO: 58. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-36 or of SEQ ID NO: 58, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-36, (b) the HVR-H2 amino acid sequence of antibody AL2p-36, and (c) the HVR-H3 amino acid sequence of antibody AL2p-36. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-36 or to the amino acid sequence of SEQ ID NO: 104 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-36 or the amino acid sequence of SEQ ID NO: 104. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-36 or the amino acid sequence of SEQ ID NO: 104. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-36 or of SEQ ID NO: 104, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1

amino acid sequence of antibody AL2p-36, (b) the HVR-L2 amino acid sequence of antibody AL2p-36, and (c) the HVR-L3 amino acid sequence of antibody AL2p-36.

[0193] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-37 or to the amino acid sequence of SEQ ID NO: 59; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-37 or to the amino acid sequence of SEQ ID NO: 104. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-37 or to the amino acid sequence of SEQ ID NO: 59, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-37. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-37 or to the amino acid sequence of SEQ ID NO: 104, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-37. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-37 or to the amino acid sequence of SEQ ID NO: 59 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-37 or the amino acid sequence of SEQ ID NO: 59. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-37 or the amino acid sequence of SEQ ID NO: 59. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the

HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-37 or of SEQ ID NO: 59, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-37, (b) the HVR-H2 amino acid sequence of antibody AL2p-37, and (c) the HVR-H3 amino acid sequence of antibody AL2p-37. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-37 or to the amino acid sequence of SEQ ID NO: 104 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-37 or the amino acid sequence of SEQ ID NO: 104. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-37 or the amino acid sequence of SEQ ID NO: 104. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-37 or of SEQ ID NO: 104, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-37, (b) the HVR-L2 amino acid sequence of antibody AL2p-37, and (c) the HVR-L3 amino acid sequence of antibody AL2p-37.

[0194] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-38 or to the amino acid sequence of SEQ ID NO: 60; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-38 or to the amino acid sequence of SEQ ID NO: 105. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at

least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-38 or to the amino acid sequence of SEQ ID NO: 60, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-38. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-38 or to the amino acid sequence of SEQ ID NO: 105, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-38. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-38 or to the amino acid sequence of SEQ ID NO: 60 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-38 or the amino acid sequence of SEQ ID NO: 60. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-38 or the amino acid sequence of SEQ ID NO: 60. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-38 or of SEQ ID NO: 60, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-38, (b) the HVR-H2 amino acid sequence of antibody AL2p-38, and (c) the HVR-H3 amino acid sequence of antibody AL2p-38. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-38 or to the amino acid sequence of SEQ ID NO: 105 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-38 or the amino acid sequence of SEQ ID NO: 105. In certain

embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-38 or the amino acid sequence of SEQ ID NO: 105. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-38 or of SEQ ID NO: 105, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-38, (b) the HVR-L2 amino acid sequence of antibody AL2p-38, and (c) the HVR-L3 amino acid sequence of antibody AL2p-38.

[0195] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-39 or to the amino acid sequence of SEQ ID NO: 60; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-39 or to the amino acid sequence of SEQ ID NO: 106. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-39 or to the amino acid sequence of SEQ ID NO: 60, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-39. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-39 or to the amino acid sequence of SEQ ID NO: 106, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-39. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-39 or to the amino acid sequence of SEQ ID NO: 60 and contains substitutions (*e.g.*, conservative substitutions,

insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-39 or the amino acid sequence of SEQ ID NO: 60. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-39 or the amino acid sequence of SEQ ID NO: 60. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-39 or of SEQ ID NO: 60, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-39, (b) the HVR-H2 amino acid sequence of antibody AL2p-39, and (c) the HVR-H3 amino acid sequence of antibody AL2p-39. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-39 or to the amino acid sequence of SEQ ID NO: 106 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-39 or the amino acid sequence of SEQ ID NO: 106. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-39 or the amino acid sequence of SEQ ID NO: 106. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-39 or of SEQ ID NO: 106, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-39, (b) the HVR-L2 amino acid sequence of antibody AL2p-39, and (c) the HVR-L3 amino acid sequence of antibody AL2p-39.

[0196] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-40 or to the amino acid sequence of SEQ ID NO: 60; and/or the light

chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-40 or to the amino acid sequence of SEQ ID NO: 107. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-40 or to the amino acid sequence of SEQ ID NO: 60, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-40. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-40 or to the amino acid sequence of SEQ ID NO: 107, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-40. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-40 or to the amino acid sequence of SEQ ID NO: 60 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-40 or the amino acid sequence of SEQ ID NO: 60. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-40 or the amino acid sequence of SEQ ID NO: 60. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-40 or of SEQ ID NO: 60, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-40, (b) the HVR-H2 amino acid sequence of antibody AL2p-40, and (c) the HVR-H3 amino acid sequence of antibody AL2p-40. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%,

at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-40 or to the amino acid sequence of SEQ ID NO: 107 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-40 or the amino acid sequence of SEQ ID NO: 107. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-40 or the amino acid sequence of SEQ ID NO: 107. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-40 or of SEQ ID NO: 107, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-40, (b) the HVR-L2 amino acid sequence of antibody AL2p-40, and (c) the HVR-L3 amino acid sequence of antibody AL2p-40.

[0197] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-41 or to the amino acid sequence of SEQ ID NO: 61; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-41 or to the amino acid sequence of SEQ ID NO: 106. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-41 or to the amino acid sequence of SEQ ID NO: 61, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-41. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-41 or to the

amino acid sequence of SEQ ID NO: 106, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-41. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-41 or to the amino acid sequence of SEQ ID NO: 61 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-41 or the amino acid sequence of SEQ ID NO: 61. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-41 or the amino acid sequence of SEQ ID NO: 61. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-41 or of SEQ ID NO: 61, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-41, (b) the HVR-H2 amino acid sequence of antibody AL2p-41, and (c) the HVR-H3 amino acid sequence of antibody AL2p-41. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-41 or to the amino acid sequence of SEQ ID NO: 106 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-41 or the amino acid sequence of SEQ ID NO: 106. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-41 or the amino acid sequence of SEQ ID NO: 106. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-41 or of SEQ ID NO: 106, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1

amino acid sequence of antibody AL2p-41, (b) the HVR-L2 amino acid sequence of antibody AL2p-41, and (c) the HVR-L3 amino acid sequence of antibody AL2p-41.

[0198] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-42 or to the amino acid sequence of SEQ ID NO: 61; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-42 or to the amino acid sequence of SEQ ID NO: 107. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-42 or to the amino acid sequence of SEQ ID NO: 61, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-42. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-42 or to the amino acid sequence of SEQ ID NO: 107, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-42. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-42 or to the amino acid sequence of SEQ ID NO: 61 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-42 or the amino acid sequence of SEQ ID NO: 61. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-42 or the amino acid sequence of SEQ ID NO: 61. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the

HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-42 or of SEQ ID NO: 61, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-42, (b) the HVR-H2 amino acid sequence of antibody AL2p-42, and (c) the HVR-H3 amino acid sequence of antibody AL2p-42. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-42 or to the amino acid sequence of SEQ ID NO: 107 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-42 or the amino acid sequence of SEQ ID NO: 107. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-42 or the amino acid sequence of SEQ ID NO: 107. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-42 or of SEQ ID NO: 107, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-42, (b) the HVR-L2 amino acid sequence of antibody AL2p-42, and (c) the HVR-L3 amino acid sequence of antibody AL2p-42.

[0199] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-43 or to the amino acid sequence of SEQ ID NO: 62; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-43 or to the amino acid sequence of SEQ ID NO: 105. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at

least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-43 or to the amino acid sequence of SEQ ID NO: 62, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-43. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-43 or to the amino acid sequence of SEQ ID NO: 105, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-43. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-43 or to the amino acid sequence of SEQ ID NO: 62 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-43 or the amino acid sequence of SEQ ID NO: 62. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-43 or the amino acid sequence of SEQ ID NO: 62. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-43 or of SEQ ID NO: 62, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-43, (b) the HVR-H2 amino acid sequence of antibody AL2p-43, and (c) the HVR-H3 amino acid sequence of antibody AL2p-43. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-43 or to the amino acid sequence of SEQ ID NO: 105 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-43 or the amino acid sequence of SEQ ID NO: 105. In certain

embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-43 or the amino acid sequence of SEQ ID NO: 105. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-43 or of SEQ ID NO: 105, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-43, (b) the HVR-L2 amino acid sequence of antibody AL2p-43, and (c) the HVR-L3 amino acid sequence of antibody AL2p-43.

[0200] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-44 or to the amino acid sequence of SEQ ID NO: 62; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-44 or to the amino acid sequence of SEQ ID NO: 107. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-44 or to the amino acid sequence of SEQ ID NO: 62, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-44. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-44 or to the amino acid sequence of SEQ ID NO: 107, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-44. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-44 or to the amino acid sequence of SEQ ID NO: 62 and contains substitutions (*e.g.*, conservative substitutions,

insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-44 or the amino acid sequence of SEQ ID NO: 62. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-44 or the amino acid sequence of SEQ ID NO: 62. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-44 or of SEQ ID NO: 62, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-44, (b) the HVR-H2 amino acid sequence of antibody AL2p-44, and (c) the HVR-H3 amino acid sequence of antibody AL2p-44. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-44 or to the amino acid sequence of SEQ ID NO: 107 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-44 or the amino acid sequence of SEQ ID NO: 107. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-44 or the amino acid sequence of SEQ ID NO: 107. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-44 or of SEQ ID NO: 107, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-44, (b) the HVR-L2 amino acid sequence of antibody AL2p-44, and (c) the HVR-L3 amino acid sequence of antibody AL2p-44.

[0201] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-45 or to the amino acid sequence of SEQ ID NO: 63; and/or the light

chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-45 or to the amino acid sequence of SEQ ID NO: 108. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-45 or to the amino acid sequence of SEQ ID NO: 63, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-45. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-45 or to the amino acid sequence of SEQ ID NO: 108, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-45. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-45 or to the amino acid sequence of SEQ ID NO: 63 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-45 or the amino acid sequence of SEQ ID NO: 63. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-45 or the amino acid sequence of SEQ ID NO: 63. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-45 or of SEQ ID NO: 63, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-45, (b) the HVR-H2 amino acid sequence of antibody AL2p-45, and (c) the HVR-H3 amino acid sequence of antibody AL2p-45. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%,

at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-45 or to the amino acid sequence of SEQ ID NO: 108 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-45 or the amino acid sequence of SEQ ID NO: 108. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-45 or the amino acid sequence of SEQ ID NO: 108. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-45 or of SEQ ID NO: 108, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-45, (b) the HVR-L2 amino acid sequence of antibody AL2p-45, and (c) the HVR-L3 amino acid sequence of antibody AL2p-45.

[0202] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-46 or to the amino acid sequence of SEQ ID NO: 63; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-46 or to the amino acid sequence of SEQ ID NO: 109. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-46 or to the amino acid sequence of SEQ ID NO: 63, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-46. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-46 or to the

amino acid sequence of SEQ ID NO: 109, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-46. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-46 or to the amino acid sequence of SEQ ID NO: 63 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-46 or the amino acid sequence of SEQ ID NO: 63. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-46 or the amino acid sequence of SEQ ID NO: 63. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-46 or of SEQ ID NO: 63, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-46, (b) the HVR-H2 amino acid sequence of antibody AL2p-46, and (c) the HVR-H3 amino acid sequence of antibody AL2p-46. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-46 or to the amino acid sequence of SEQ ID NO: 109 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-46 or the amino acid sequence of SEQ ID NO: 109. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-46 or the amino acid sequence of SEQ ID NO: 109. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-46 or of SEQ ID NO: 109, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1

amino acid sequence of antibody AL2p-46, (b) the HVR-L2 amino acid sequence of antibody AL2p-46, and (c) the HVR-L3 amino acid sequence of antibody AL2p-46.

[0203] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-47 or to the amino acid sequence of SEQ ID NO: 64; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-47 or to the amino acid sequence of SEQ ID NO: 108. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-47 or to the amino acid sequence of SEQ ID NO: 64, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-47. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-47 or to the amino acid sequence of SEQ ID NO: 108, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-47. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-47 or to the amino acid sequence of SEQ ID NO: 64 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-47 or the amino acid sequence of SEQ ID NO: 64. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-47 or the amino acid sequence of SEQ ID NO: 64. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the

HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-47 or of SEQ ID NO: 64, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-47, (b) the HVR-H2 amino acid sequence of antibody AL2p-47, and (c) the HVR-H3 amino acid sequence of antibody AL2p-47. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-47 or to the amino acid sequence of SEQ ID NO: 108 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-47 or the amino acid sequence of SEQ ID NO: 108. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-47 or the amino acid sequence of SEQ ID NO: 108. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-47 or of SEQ ID NO: 108, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-47, (b) the HVR-L2 amino acid sequence of antibody AL2p-47, and (c) the HVR-L3 amino acid sequence of antibody AL2p-47.

[0204] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-48 or to the amino acid sequence of SEQ ID NO: 64; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-48 or to the amino acid sequence of SEQ ID NO: 109. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at

least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-48 or to the amino acid sequence of SEQ ID NO: 64, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-48. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-48 or to the amino acid sequence of SEQ ID NO: 109, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-48. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-48 or to the amino acid sequence of SEQ ID NO: 64 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-48 or the amino acid sequence of SEQ ID NO: 64. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-48 or the amino acid sequence of SEQ ID NO: 64. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-48 or of SEQ ID NO: 64, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-48, (b) the HVR-H2 amino acid sequence of antibody AL2p-48, and (c) the HVR-H3 amino acid sequence of antibody AL2p-48. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-48 or to the amino acid sequence of SEQ ID NO: 109 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-48 or the amino acid sequence of SEQ ID NO: 109. In certain

embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-48 or the amino acid sequence of SEQ ID NO: 109. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-48 or of SEQ ID NO: 109, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-48, (b) the HVR-L2 amino acid sequence of antibody AL2p-48, and (c) the HVR-L3 amino acid sequence of antibody AL2p-48.

[0205] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-49 or to the amino acid sequence of SEQ ID NO: 65; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-49 or to the amino acid sequence of SEQ ID NO: 109. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-49 or to the amino acid sequence of SEQ ID NO: 65, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-49. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-49 or to the amino acid sequence of SEQ ID NO: 109, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-49. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-49 or to the amino acid sequence of SEQ ID NO: 65 and contains substitutions (*e.g.*, conservative substitutions,

insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-49 or the amino acid sequence of SEQ ID NO: 65. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-49 or the amino acid sequence of SEQ ID NO: 65. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-49 or of SEQ ID NO: 65, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-49, (b) the HVR-H2 amino acid sequence of antibody AL2p-49, and (c) the HVR-H3 amino acid sequence of antibody AL2p-49. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-49 or to the amino acid sequence of SEQ ID NO: 109 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-49 or the amino acid sequence of SEQ ID NO: 109. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-49 or the amino acid sequence of SEQ ID NO: 109. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-49 or of SEQ ID NO: 109, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-49, (b) the HVR-L2 amino acid sequence of antibody AL2p-49, and (c) the HVR-L3 amino acid sequence of antibody AL2p-49.

[0206] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-50 or to the amino acid sequence of SEQ ID NO: 66; and/or the light

chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-50 or to the amino acid sequence of SEQ ID NO: 108. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-50 or to the amino acid sequence of SEQ ID NO: 66, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-50. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-50 or to the amino acid sequence of SEQ ID NO: 108, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-50. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-50 or to the amino acid sequence of SEQ ID NO: 66 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-50 or the amino acid sequence of SEQ ID NO: 66. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-50 or the amino acid sequence of SEQ ID NO: 66. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-50 or of SEQ ID NO: 66, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-50, (b) the HVR-H2 amino acid sequence of antibody AL2p-50, and (c) the HVR-H3 amino acid sequence of antibody AL2p-50. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%,

at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-50 or to the amino acid sequence of SEQ ID NO: 108 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-50 or the amino acid sequence of SEQ ID NO: 108. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-50 or the amino acid sequence of SEQ ID NO: 108. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-50 or of SEQ ID NO: 108, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-50, (b) the HVR-L2 amino acid sequence of antibody AL2p-50, and (c) the HVR-L3 amino acid sequence of antibody AL2p-50.

[0207] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-51 or to the amino acid sequence of SEQ ID NO: 66; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-51 or to the amino acid sequence of SEQ ID NO: 109. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-51 or to the amino acid sequence of SEQ ID NO: 66, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-51. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-51 or to the

amino acid sequence of SEQ ID NO: 109, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-51. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-51 or to the amino acid sequence of SEQ ID NO: 66 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-51 or the amino acid sequence of SEQ ID NO: 66. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-51 or the amino acid sequence of SEQ ID NO: 66. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-51 or of SEQ ID NO: 66, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-51, (b) the HVR-H2 amino acid sequence of antibody AL2p-51, and (c) the HVR-H3 amino acid sequence of antibody AL2p-51. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-51 or to the amino acid sequence of SEQ ID NO: 109 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-51 or the amino acid sequence of SEQ ID NO: 109. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-51 or the amino acid sequence of SEQ ID NO: 109. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-51 or of SEQ ID NO: 109, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1

amino acid sequence of antibody AL2p-51, (b) the HVR-L2 amino acid sequence of antibody AL2p-51, and (c) the HVR-L3 amino acid sequence of antibody AL2p-51.

[0208] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-52 or to the amino acid sequence of SEQ ID NO: 67; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-52 or to the amino acid sequence of SEQ ID NO: 108. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-52 or to the amino acid sequence of SEQ ID NO: 67, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-52. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-52 or to the amino acid sequence of SEQ ID NO: 108, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-52. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-52 or to the amino acid sequence of SEQ ID NO: 67 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-52 or the amino acid sequence of SEQ ID NO: 67. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-52 or the amino acid sequence of SEQ ID NO: 67. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the

HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-52 or of SEQ ID NO: 67, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-52, (b) the HVR-H2 amino acid sequence of antibody AL2p-52, and (c) the HVR-H3 amino acid sequence of antibody AL2p-52. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-52 or to the amino acid sequence of SEQ ID NO: 108 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-52 or the amino acid sequence of SEQ ID NO: 108. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-52 or the amino acid sequence of SEQ ID NO: 108. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-52 or of SEQ ID NO: 108, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-52, (b) the HVR-L2 amino acid sequence of antibody AL2p-52, and (c) the HVR-L3 amino acid sequence of antibody AL2p-52.

[0209] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-53 or to the amino acid sequence of SEQ ID NO: 67; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-53 or to the amino acid sequence of SEQ ID NO: 109. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at

least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-53 or to the amino acid sequence of SEQ ID NO: 67, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-53. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-53 or to the amino acid sequence of SEQ ID NO: 109, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-53. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-53 or to the amino acid sequence of SEQ ID NO: 67 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-53 or the amino acid sequence of SEQ ID NO: 67. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-53 or the amino acid sequence of SEQ ID NO: 67. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-53 or of SEQ ID NO: 67, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-53, (b) the HVR-H2 amino acid sequence of antibody AL2p-53, and (c) the HVR-H3 amino acid sequence of antibody AL2p-53. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-53 or to the amino acid sequence of SEQ ID NO: 109 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-53 or the amino acid sequence of SEQ ID NO: 109. In certain

embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-53 or the amino acid sequence of SEQ ID NO: 109. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-53 or of SEQ ID NO: 109, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-53, (b) the HVR-L2 amino acid sequence of antibody AL2p-53, and (c) the HVR-L3 amino acid sequence of antibody AL2p-53.

[0210] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-54 or to the amino acid sequence of SEQ ID NO: 68; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-54 or to the amino acid sequence of SEQ ID NO: 109. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-54 or to the amino acid sequence of SEQ ID NO: 68, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-54. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-54 or to the amino acid sequence of SEQ ID NO: 109, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-54. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-54 or to the amino acid sequence of SEQ ID NO: 68 and contains substitutions (*e.g.*, conservative substitutions,

insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-54 or the amino acid sequence of SEQ ID NO: 68. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-54 or the amino acid sequence of SEQ ID NO: 68. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-54 or of SEQ ID NO: 68, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-54, (b) the HVR-H2 amino acid sequence of antibody AL2p-54, and (c) the HVR-H3 amino acid sequence of antibody AL2p-54. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-54 or to the amino acid sequence of SEQ ID NO: 109 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-54 or the amino acid sequence of SEQ ID NO: 109. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-54 or the amino acid sequence of SEQ ID NO: 109. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-54 or of SEQ ID NO: 109, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-54, (b) the HVR-L2 amino acid sequence of antibody AL2p-54, and (c) the HVR-L3 amino acid sequence of antibody AL2p-54.

[0211] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-55 or to the amino acid sequence of SEQ ID NO: 69; and/or the light

chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-55 or to the amino acid sequence of SEQ ID NO: 108. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-55 or to the amino acid sequence of SEQ ID NO: 69, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-55. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-55 or to the amino acid sequence of SEQ ID NO: 108, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-55. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-55 or to the amino acid sequence of SEQ ID NO: 69 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-55 or the amino acid sequence of SEQ ID NO: 69. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-55 or the amino acid sequence of SEQ ID NO: 69. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-55 or of SEQ ID NO: 69, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-55, (b) the HVR-H2 amino acid sequence of antibody AL2p-55, and (c) the HVR-H3 amino acid sequence of antibody AL2p-55. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%,

at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-55 or to the amino acid sequence of SEQ ID NO: 108 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-55 or the amino acid sequence of SEQ ID NO: 108. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-55 or the amino acid sequence of SEQ ID NO: 108. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-55 or of SEQ ID NO: 108, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-55, (b) the HVR-L2 amino acid sequence of antibody AL2p-55, and (c) the HVR-L3 amino acid sequence of antibody AL2p-55.

[0212] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-56 or to the amino acid sequence of SEQ ID NO: 69; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-56 or to the amino acid sequence of SEQ ID NO: 108. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-56 or to the amino acid sequence of SEQ ID NO: 69, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-56. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-56 or to the

amino acid sequence of SEQ ID NO: 108, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-56. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-56 or to the amino acid sequence of SEQ ID NO: 69 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-56 or the amino acid sequence of SEQ ID NO: 69. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-56 or the amino acid sequence of SEQ ID NO: 69. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-56 or of SEQ ID NO: 69, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-56, (b) the HVR-H2 amino acid sequence of antibody AL2p-56, and (c) the HVR-H3 amino acid sequence of antibody AL2p-56. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-56 or to the amino acid sequence of SEQ ID NO: 108 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-56 or the amino acid sequence of SEQ ID NO: 108. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-56 or the amino acid sequence of SEQ ID NO: 108. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-56 or of SEQ ID NO: 108, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1

amino acid sequence of antibody AL2p-56, (b) the HVR-L2 amino acid sequence of antibody AL2p-56, and (c) the HVR-L3 amino acid sequence of antibody AL2p-56.

[0213] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-57 or to the amino acid sequence of SEQ ID NO: 69; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-57 or to the amino acid sequence of SEQ ID NO: 109. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-57 or to the amino acid sequence of SEQ ID NO: 69, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-57. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-57 or to the amino acid sequence of SEQ ID NO: 109, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-57. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-57 or to the amino acid sequence of SEQ ID NO: 69 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-57 or the amino acid sequence of SEQ ID NO: 69. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-57 or the amino acid sequence of SEQ ID NO: 69. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the

HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-57 or of SEQ ID NO: 69, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-57, (b) the HVR-H2 amino acid sequence of antibody AL2p-57, and (c) the HVR-H3 amino acid sequence of antibody AL2p-57. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-57 or to the amino acid sequence of SEQ ID NO: 109 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-57 or the amino acid sequence of SEQ ID NO: 109. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-57 or the amino acid sequence of SEQ ID NO: 109. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-57 or of SEQ ID NO: 109, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-57, (b) the HVR-L2 amino acid sequence of antibody AL2p-57, and (c) the HVR-L3 amino acid sequence of antibody AL2p-57.

[0214] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-58 or to the amino acid sequence of SEQ ID NO: 59; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-58 or to the amino acid sequence of SEQ ID NO: 112. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at

least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-58 or to the amino acid sequence of SEQ ID NO: 59, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-58. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-58 or to the amino acid sequence of SEQ ID NO: 112, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-58. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-58 or to the amino acid sequence of SEQ ID NO: 59 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-58 or the amino acid sequence of SEQ ID NO: 59. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-58 or the amino acid sequence of SEQ ID NO: 59. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-58 or of SEQ ID NO: 59, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-58, (b) the HVR-H2 amino acid sequence of antibody AL2p-58, and (c) the HVR-H3 amino acid sequence of antibody AL2p-58. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-58 or to the amino acid sequence of SEQ ID NO: 112 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-58 or the amino acid sequence of SEQ ID NO: 112. In certain

embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-58 or the amino acid sequence of SEQ ID NO: 112. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-58 or of SEQ ID NO: 112, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-58, (b) the HVR-L2 amino acid sequence of antibody AL2p-58, and (c) the HVR-L3 amino acid sequence of antibody AL2p-58.

[0215] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-59 or to the amino acid sequence of SEQ ID NO: 91; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-59 or to the amino acid sequence of SEQ ID NO: 118. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-59 or to the amino acid sequence of SEQ ID NO: 91, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-59. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-59 or to the amino acid sequence of SEQ ID NO: 118, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-59. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-59 or to the amino acid sequence of SEQ ID NO: 91 and contains substitutions (*e.g.*, conservative substitutions,

insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-59 or the amino acid sequence of SEQ ID NO: 91. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-59 or the amino acid sequence of SEQ ID NO: 91. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-59 or of SEQ ID NO: 91, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-59, (b) the HVR-H2 amino acid sequence of antibody AL2p-59, and (c) the HVR-H3 amino acid sequence of antibody AL2p-59. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-59 or to the amino acid sequence of SEQ ID NO: 118 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-59 or the amino acid sequence of SEQ ID NO: 118. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-59 or the amino acid sequence of SEQ ID NO: 118. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-59 or of SEQ ID NO: 118, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-59, (b) the HVR-L2 amino acid sequence of antibody AL2p-59, and (c) the HVR-L3 amino acid sequence of antibody AL2p-59.

[0216] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-60 or to the amino acid sequence of SEQ ID NO: 53; and/or the light

chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-60 or to the amino acid sequence of SEQ ID NO: 113. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-60 or to the amino acid sequence of SEQ ID NO: 53, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-60. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-60 or to the amino acid sequence of SEQ ID NO: 113, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-60. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-60 or to the amino acid sequence of SEQ ID NO: 53 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-60 or the amino acid sequence of SEQ ID NO: 53. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-60 or the amino acid sequence of SEQ ID NO: 53. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-60 or of SEQ ID NO: 53, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-60, (b) the HVR-H2 amino acid sequence of antibody AL2p-60, and (c) the HVR-H3 amino acid sequence of antibody AL2p-60. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%,

at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-60 or to the amino acid sequence of SEQ ID NO: 113 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-60 or the amino acid sequence of SEQ ID NO: 113. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-60 or the amino acid sequence of SEQ ID NO: 113. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-60 or of SEQ ID NO: 113, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-60, (b) the HVR-L2 amino acid sequence of antibody AL2p-60, and (c) the HVR-L3 amino acid sequence of antibody AL2p-60.

[0217] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-61 or to the amino acid sequence of SEQ ID NO: 70; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-61 or to the amino acid sequence of SEQ ID NO: 110. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-61 or to the amino acid sequence of SEQ ID NO: 70, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-61. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-61 or to the

amino acid sequence of SEQ ID NO: 110, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-61. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-61 or to the amino acid sequence of SEQ ID NO: 70 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-61 or the amino acid sequence of SEQ ID NO: 70. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-61 or the amino acid sequence of SEQ ID NO: 70. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-61 or of SEQ ID NO: 70, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-61, (b) the HVR-H2 amino acid sequence of antibody AL2p-61, and (c) the HVR-H3 amino acid sequence of antibody AL2p-61. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-61 or to the amino acid sequence of SEQ ID NO: 110 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-61 or the amino acid sequence of SEQ ID NO: 110. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-61 or the amino acid sequence of SEQ ID NO: 110. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-61 or of SEQ ID NO: 110, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1

amino acid sequence of antibody AL2p-61, (b) the HVR-L2 amino acid sequence of antibody AL2p-61, and (c) the HVR-L3 amino acid sequence of antibody AL2p-61.

[0218] In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain and a heavy chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-62 or to the amino acid sequence of SEQ ID NO: 71; and/or the light chain variable domain comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-62 or to the amino acid sequence of SEQ ID NO: 111. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a heavy chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-62 or to the amino acid sequence of SEQ ID NO: 71, wherein the heavy chain variable domain comprises the HVR-H1, HVR-H2, and HVR-H3 amino acid sequences of antibody AL2p-62. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain comprising an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-62 or to the amino acid sequence of SEQ ID NO: 111, wherein the light chain variable domain comprises the HVR-L1, HVR-L2, and HVR-L3 amino acid sequences of antibody AL2p-62. In some embodiments, the anti-TREM2 antibody comprises a heavy chain variable domain (VH) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a heavy chain variable domain amino acid sequence of antibody AL2p-62 or to the amino acid sequence of SEQ ID NO: 71 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-62 or the amino acid sequence of SEQ ID NO: 71. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the heavy chain variable domain amino acid sequence of antibody AL2p-62 or the amino acid sequence of SEQ ID NO: 71. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the

HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VH sequence of antibody AL2p-62 or of SEQ ID NO: 71, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) the HVR-H1 amino acid sequence of antibody AL2p-62, (b) the HVR-H2 amino acid sequence of antibody AL2p-62, and (c) the HVR-H3 amino acid sequence of antibody AL2p-62. In some embodiments, anti-TREM2 antibodies of the present disclosure comprise a light chain variable domain (VL) sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to a light chain variable domain amino acid sequence of antibody AL2p-62 or to the amino acid sequence of SEQ ID NO: 111 and contains substitutions (*e.g.*, conservative substitutions, insertions, or deletions relative to the reference sequence), but the anti-TREM2 antibody comprising that sequence retains the ability to bind to TREM2. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-62 or the amino acid sequence of SEQ ID NO: 111. In certain embodiments, a total of 1 to 5 amino acids have been substituted, inserted and/or deleted in the light chain variable domain amino acid sequence of antibody AL2p-62 or the amino acid sequence of SEQ ID NO: 111. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (*i.e.*, in the FR regions). In some embodiments, the substitutions, insertions, or deletions occur in in the FR regions. Optionally, the anti-TREM2 antibody comprises the VL sequence of antibody AL2p-62 or of SEQ ID NO: 111, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) the HVR-L1 amino acid sequence of antibody AL2p-62, (b) the HVR-L2 amino acid sequence of antibody AL2p-62, and (c) the HVR-L3 amino acid sequence of antibody AL2p-62.

[0219] In some embodiments, the anti-TREM2 antibody is provided, wherein the antibody comprises a VH as in any of the embodiments provided above, and a VL as in any of the embodiments provided above. In some embodiments, provided herein are anti-TREM2antibodies, wherein the antibody comprises a VH as in any of the embodiments provided above, and a VL as in any of the embodiments provided above. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NOs: 27-71 and 91 and SEQ ID NOs: 92-113 and 118, respectively, including post-translational modifications of those sequences.

[0220] In some embodiments, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 53, and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 97. In some embodiments, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 59; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 104. In some embodiments, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 64;

and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 108. In some embodiments, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 70; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 110. In some embodiments, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 71; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 111. In some embodiments, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 59; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 112. In some embodiments, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 53; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 113.

[0221] Any of the antibodies of the present disclosure may be produced by a cell line. In some embodiments, the cell line may be a mammalian cell line. In certain embodiments, the cell line may be a hybridoma cell line. In other embodiments, the cell line may be a yeast cell line. Any cell line known in the art suitable for antibody production may be used to produce an antibody of the present disclosure. Exemplary cell lines for antibody production are described throughout the present disclosure.

[0222] In some embodiments, the anti-TREM2 antibody is an anti-TREM2 monoclonal antibody selected from 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.

[0223] In some embodiments, the anti-TREM2 antibody is anti-TREM2 monoclonal antibody AL2p-31. In some embodiments, the anti-TREM2 antibody is an isolated antibody which binds essentially the same TREM2 epitope as AL2p-31. In some embodiments, the anti-TREM2 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody AL2p-31. In some embodiments, the anti-TREM2 antibody is an isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody AL2p-31. In some embodiments, the anti-TREM2 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain and

the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody AL2p-31.

[0224] In some embodiments, the anti-TREM2 antibody is anti-TREM2 monoclonal antibody AL2p-37. In some embodiments, the anti-TREM2 antibody is an isolated antibody which binds essentially the same TREM2 epitope as AL2p-37. In some embodiments, the anti-TREM2 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody AL2p-37. In some embodiments, the anti-TREM2 antibody is an isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody AL2p-37. In some embodiments, the anti-TREM2 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody AL2p-37.

[0225] In some embodiments, the anti-TREM2 antibody is anti-TREM2 monoclonal antibody AL2p-47. In some embodiments, the anti-TREM2 antibody is an isolated antibody which binds essentially the same TREM2 epitope as AL2p-47. In some embodiments, the anti-TREM2 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody AL2p-47. In some embodiments, the anti-TREM2 antibody is an isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody AL2p-47. In some embodiments, the anti-TREM2 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody AL2p-47.

[0226] In some embodiments, the anti-TREM2 antibody is anti-TREM2 monoclonal antibody AL2p-58. In some embodiments, the anti-TREM2 antibody is an isolated antibody which binds essentially the same TREM2 epitope as AL2p-58. In some embodiments, the anti-TREM2 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody AL2p-58. In some embodiments, the anti-TREM2 antibody is an isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody AL2p-58. In some embodiments, the anti-TREM2 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody AL2p-58.

[0227] In some embodiments, the anti-TREM2 antibody is anti-TREM2 monoclonal antibody AL2p-60. In some embodiments, the anti-TREM2 antibody is an isolated antibody which binds essentially the same TREM2 epitope as AL2p-60. In some embodiments, the anti-TREM2 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody AL2p-60. In some embodiments, the anti-TREM2 antibody is an

isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody AL2p-60. In some embodiments, the anti-TREM2 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody AL2p-60.

[0228] In some embodiments, the anti-TREM2 antibody is anti-TREM2 monoclonal antibody AL2p-61. In some embodiments, the anti-TREM2 antibody is an isolated antibody which binds essentially the same TREM2 epitope as AL2p-61. In some embodiments, the anti-TREM2 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody AL2p-61. In some embodiments, the anti-TREM2 antibody is an isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody AL2p-61. In some embodiments, the anti-TREM2 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody AL2p-61.

[0229] In some embodiments, the anti-TREM2 antibody is anti-TREM2 monoclonal antibody AL2p-62. In some embodiments, the anti-TREM2 antibody is an isolated antibody which binds essentially the same TREM2 epitope as AL2p-62. In some embodiments, the anti-TREM2 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain of monoclonal antibody AL2p-62. In some embodiments, the anti-TREM2 antibody is an isolated antibody comprising the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody AL2p-62. In some embodiments, the anti-TREM2 antibody is an isolated antibody comprising the HVR-H1, HVR-H2, and HVR-H3 of the heavy chain variable domain and the HVR-L1, HVR-L2, and HVR-L3 of the light chain variable domain of monoclonal antibody AL2p-62.

[0230] In some embodiments, anti-TREM2 antibodies of the present disclosure do not compete with one or more TREM2 ligands for binding to TREM2. In some embodiments, anti-TREM2 antibodies of the present disclosure are capable of binding TREM2 without blocking simultaneous binding of one or moreTREM2 ligands to TREM2. In some embodiments anti-TREM2 antibodies of the present disclosure are capable of additive and/or synergistic functional interactions with one or more TREM2 ligands. In some embodiments, anti-TREM2 antibodies of the present disclosure increase the maximal activity of TREM2 exposed to saturating concentrations of one or more TREM2 ligands. In some embodiments, anti-TREM2 antibodies of the present disclosure increase the activity of TREM2 obtained at any concentration of one or more TREM2 ligands.

Anti-TREM2 antibody binding affinity

[0231] The dissociation constants (K_D) of anti-TREM2 antibodies for human TREM2 and cynomolgus monkey TREM2 may be at least 1-fold lower, at least 2-fold lower, at least 3-fold lower,

at least 4-fold lower, at least 5-fold lower, at least 6-fold lower, at least 7-fold lower, at least 8-fold lower, at least 9-fold lower, at least 10-fold lower, at least 11-fold lower, at least 12-fold lower, at least 13-fold lower, at least 14-fold lower, at least 15-fold lower, at least 16-fold lower, at least 17-fold lower, at least 18-fold lower, at least 19-fold lower, at least 20-fold lower or lower 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 comprising 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 embodiments, the dissociation constant (K_D) is determined at a temperature of approximately 25°C. In some embodiments, the K_D is determined using a monovalent antibody (*e.g.*, a Fab) or a full-length antibody in a monovalent form. Methods for the preparation and selection of antibodies that interact and/or bind with specificity to TREM2 are described herein. (*e.g.*, see **Examples 1 and 2**).

[0232] In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for human TREM2 may range from about 300 nM to about 100 pM, from about 200 nM to about 100 pM, from about 100 nM to about 100 pM, from about 90 nM to about 100 pM, from about 80 nM to about 100 pM, from about 70 nM to about 100 pM, from about 60 nM to about 100 pM, from about 50 nM to about 100 pM, from about 40 nM to about 100 pM, from about 30 nM to about 100 pM, from about 20 nM to about 100 pM, from about 10 nM to about 100 pM, from about 9 nM to about 100 pM, from about 8 nM to about 100 pM, from about 7 nM to about 100 pM, from about 6 nM to about 100 pM, from about 5 nM to about 100 pM, from about 4 nM to about 100 pM, from about 3 nM to about 100 pM, from about 2 nM to about 100 pM, from about 1 nM to about 100 pM, from 900 pM to about 100 pM, from about 800 pM to about 100 pM, from 700 pM to about 100 pM, from 600 pM to about 500 pM, from 400 pM to about 100 pM, from 300 pM to about 100 pM, from 200 pM to about 100 pM, from 900 pM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constant (K_D) is determined at a temperature of approximately 25°C. In some embodiments, the K_D is determined using a monovalent antibody (*e.g.*, a Fab) or a full-length antibody in a monovalent form. Methods for the preparation and selection of antibodies that interact and/or bind with specificity to TREM2 are described herein. (*e.g.*, see **Examples 1 and 2**).

[0233] In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for human TREM2 may range from about 300 nM to about 90 pM, from about 300 nM to about 80 pM, from about 300 nM to about 70 pM, from about 300 nM to about 60 pM, from about 300 nM to about 50 pM, from about 300 nM to about 40 pM, from about 300 nM to about 30 pM, from about 300 nM to about 20 pM, from about 300 nM to about 10 pM, from about 300 nM to about 9 pM, from about 300 nM to about 8 pM, from about 300 nM to about 7 pM, from about 300 nM to about 6 pM, from

about 300 nM to about 5 pM, from about 300 nM to about 4 pM, from about 300 nM to about 3 pM, from about 300 nM to about 2 pM, from about 300 nM to about 1 pM, or less than 1 pM. The dissociation constants (K_D) of anti-TREM2 antibodies for human TREM2 may range from about 200 nM to about 90 pM, from about 200 nM to about 80 pM, from about 200 nM to about 70 pM, from about 200 nM to about 60 pM, from about 200 nM to about 50 pM, from about 200 nM to about 40 pM, from about 200 nM to about 30 pM, from about 200 nM to about 20 pM, from about 200 nM to about 10 pM, from about 200 nM to about 9 pM, from about 200 nM to about 8 pM, from about 200 nM to about 7 pM, from about 200 nM to about 6 pM, from about 200 nM to about 5 pM, from about 200 nM to about 4 pM, from about 200 nM to about 3 pM, from about 200 nM to about 2 pM, from about 200 nM to about 1 pM, or less than 1 pM. The dissociation constants (K_D) of anti-TREM2 antibodies for human TREM2 may range from about 100 nM to about 90 pM, from about 100 nM to about 80 pM, from about 100 nM to about 70 pM, from about 100 nM to about 60 pM, from about 100 nM to about 50 pM, from about 100 nM to about 40 pM, from about 100 nM to about 30 pM, from about 100 nM to about 20 pM, from about 100 nM to about 10 pM, from about 100 nM to about 9 pM, from about 100 nM to about 8 pM, from about 100 nM to about 7 pM, from about 100 nM to about 6 pM, from about 100 nM to about 5 pM, from about 100 nM to about 4 pM, from about 100 nM to about 3 pM, from about 100 nM to about 2 pM, from about 100 nM to about 1 pM, or less than 1 pM. The dissociation constants (K_D) of anti-TREM2 antibodies for human TREM2 may range from about 90 nM to about 90 pM, from about 90 nM to about 80 pM, from about 90 nM to about 70 pM, from about 90 nM to about 60 pM, from about 90 nM to about 50 pM, from about 90 nM to about 40 pM, from about 90 nM to about 30 pM, from about 90 nM to about 20 pM, from about 90 nM to about 10 pM, from about 90 nM to about 9 pM, from about 90 nM to about 8 pM, from about 90 nM to about 7 pM, from about 90 nM to about 6 pM, from about 90 nM to about 5 pM, from about 90 nM to about 4 pM, from about 90 nM to about 3 pM, from about 90 nM to about 2 pM, from about 90 nM to about 1 pM, or less than 1 pM. The dissociation constants (K_D) of anti-TREM2 antibodies for human TREM2 may range from about 80 nM to about 90 pM, from about 80 nM to about 80 pM, from about 80 nM to about 70 pM, from about 80 nM to about 60 pM, from about 80 nM to about 50 pM, from about 80 nM to about 40 pM, from about 80 nM to about 30 pM, from about 80 nM to about 20 pM, from about 80 nM to about 10 pM, from about 80 nM to about 9 pM, from about 80 nM to about 8 pM, from about 80 nM to about 7 pM, from about 80 nM to about 6 pM, from about 80 nM to about 5 pM, from about 80 nM to about 4 pM, from about 80 nM to about 3 pM, from about 80 nM to about 2 pM, from about 80 nM to about 1 pM, or less than 1 pM. The dissociation constants (K_D) of anti-TREM2 antibodies for human TREM2 may range from about 70 nM to about 90 pM, from about 70 nM to about 80 pM, from about 70 nM to about 70 pM, from about 70 nM to about 60 pM, from about 70 nM to about 50 pM, from about 70 nM to about 40 pM, from about 70 nM to about 30 pM, from about 70 nM to about 20 pM, from about 70 nM to about 10 pM, from about 70 nM to about 9 pM, from about 70 nM to about 8 pM, from about 70 nM to about 7 pM, from about 70 nM to

about 6 pM, from about 70 nM to about 5 pM, from about 70 nM to about 4 pM, from about 70 nM to about 3 pM, from about 70 nM to about 2 pM, from about 70 nM to about 1 pM, or less than 1 pM. The dissociation constants (K_D) of anti-TREM2 antibodies for human TREM2 may range from about 60 nM to about 90 pM, from about 60 nM to about 80 pM, from about 60 nM to about 70 pM, from about 60 nM to about 60 pM, from about 60 nM to about 50 pM, from about 60 nM to about 40 pM, from about 60 nM to about 30 pM, from about 60 nM to about 20 pM, from about 60 nM to about 10 pM, from about 60 nM to about 9 pM, from about 60 nM to about 8 pM, from about 60 nM to about 7 pM, from about 60 nM to about 6 pM, from about 60 nM to about 5 pM, from about 60 nM to about 4 pM, from about 60 nM to about 3 pM, from about 60 nM to about 2 pM, from about 60 nM to about 1 pM, or less than 1 pM. The dissociation constants (K_D) of anti-TREM2 antibodies for human TREM2 may range from about 50 nM to about 90 pM, from about 50 nM to about 80 pM, from about 50 nM to about 70 pM, from about 50 nM to about 60 pM, from about 50 nM to about 50 pM, from about 50 nM to about 40 pM, from about 50 nM to about 30 pM, from about 50 nM to about 20 pM, from about 50 nM to about 10 pM, from about 50 nM to about 9 pM, from about 50 nM to about 8 pM, from about 50 nM to about 7 pM, from about 50 nM to about 6 pM, from about 50 nM to about 5 pM, from about 50 nM to about 4 pM, from about 50 nM to about 3 pM, from about 50 nM to about 2 pM, from about 50 nM to about 1 pM, or less than 1 pM. The dissociation constants (K_D) of anti-TREM2 antibodies for human TREM2 may range from about 40 nM to about 90 pM, from about 40 nM to about 80 pM, from about 40 nM to about 70 pM, from about 40 nM to about 60 pM, from about 40 nM to about 50 pM, from about 40 nM to about 40 pM, from about 40 nM to about 30 pM, from about 40 nM to about 20 pM, from about 40 nM to about 10 pM, from about 40 nM to about 9 pM, from about 40 nM to about 8 pM, from about 40 nM to about 7 pM, from about 40 nM to about 6 pM, from about 40 nM to about 5 pM, from about 40 nM to about 4 pM, from about 40 nM to about 3 pM, from about 40 nM to about 2 pM, from about 40 nM to about 1 pM, or less than 1 pM. The dissociation constants (K_D) of anti-TREM2 antibodies for human TREM2 may range from about 30 nM to about 90 pM, from about 30 nM to about 80 pM, from about 30 nM to about 70 pM, from about 30 nM to about 60 pM, from about 30 nM to about 50 pM, from about 30 nM to about 40 pM, from about 30 nM to about 30 pM, from about 30 nM to about 20 pM, from about 30 nM to about 10 pM, from about 30 nM to about 9 pM, from about 30 nM to about 8 pM, from about 30 nM to about 7 pM, from about 30 nM to about 6 pM, from about 30 nM to about 5 pM, from about 30 nM to about 4 pM, from about 30 nM to about 3 pM, from about 30 nM to about 2 pM, from about 30 nM to about 1 pM, or less than 1 pM. The dissociation constants (K_D) of anti-TREM2 antibodies for human TREM2 may range from about 20 nM to about 90 pM, from about 20 nM to about 80 pM, from about 20 nM to about 70 pM, from about 20 nM to about 60 pM, from about 20 nM to about 50 pM, from about 20 nM to about 40 pM, from about 20 nM to about 30 pM, from about 20 nM to about 20 pM, from about 20 nM to about 10 pM, from about 20 nM to about 9 pM, from about 20 nM to about 8 pM, from about 20 nM to about 7 pM, from about 20 nM to about 6 pM, from about 20 nM to about 5 pM,

from about 20 nM to about 4 pM, from about 20 nM to about 3 pM, from about 20 nM to about 2 pM, from about 20 nM to about 1 pM, or less than 1 pM. The dissociation constants (K_D) of anti-TREM2 antibodies for human TREM2 may range from about 10 nM to about 90 pM, from about 10 nM to about 80 pM, from about 10 nM to about 70 pM, from about 10 nM to about 60 pM, from about 10 nM to about 50 pM, from about 10 nM to about 40 pM, from about 10 nM to about 30 pM, from about 10 nM to about 20 pM, from about 10 nM to about 10 pM, from about 10 nM to about 9 pM, from about 10 nM to about 8 pM, from about 10 nM to about 7 pM, from about 10 nM to about 6 pM, from about 10 nM to about 5 pM, from about 10 nM to about 4 pM, from about 10 nM to about 3 pM, from about 10 nM to about 2 pM, from about 10 nM to about 1 pM, or less than 1 pM. The dissociation constants (K_D) of anti-TREM2 antibodies for human TREM2 may range from about 5 nM to about 90 pM, from about 5 nM to about 80 pM, from about 5 nM to about 70 pM, from about 5 nM to about 60 pM, from about 5 nM to about 50 pM, from about 5 nM to about 40 pM, from about 5 nM to about 30 pM, from about 5 nM to about 20 pM, from about 5 nM to about 10 pM, from about 5 nM to about 9 pM, from about 5 nM to about 8 pM, from about 5 nM to about 7 pM, from about 5 nM to about 6 pM, from about 5 nM to about 5 pM, from about 5 nM to about 4 pM, from about 5 nM to about 3 pM, from about 5 nM to about 2 pM, from about 5 nM to about 1 pM, or less than 1 pM. The dissociation constants (K_D) of anti-TREM2 antibodies for human TREM2 may range from about 1 nM to about 90 pM, from about 1 nM to about 80 pM, from about 1 nM to about 70 pM, from about 1 nM to about 60 pM, from about 1 nM to about 50 pM, from about 1 nM to about 40 pM, from about 1 nM to about 30 pM, from about 1 nM to about 20 pM, from about 1 nM to about 10 pM, from about 1 nM to about 9 pM, from about 1 nM to about 8 pM, from about 1 nM to about 7 pM, from about 1 nM to about 6 pM, from about 1 nM to about 5 pM, from about 1 nM to about 4 pM, from about 1 nM to about 3 pM, from about 1 nM to about 2 pM, from about 1 nM to about 1 pM, or less than 1 pM. The dissociation constants (K_D) of anti-TREM2 antibodies for human TREM2 may range from about 500 pM to about 90 pM, from about 500 pM to about 80 pM, from about 500 pM to about 70 pM, from about 500 pM to about 60 pM, from about 500 pM to about 50 pM, from about 500 pM to about 40 pM, from about 500 pM to about 30 pM, from about 500 pM to about 20 pM, from about 500 pM to about 10 pM, from about 500 pM to about 9 pM, from about 500 pM to about 8 pM, from about 500 pM to about 7 pM, from about 500 pM to about 6 pM, from about 500 pM to about 5 pM, from about 500 pM to about 4 pM, from about 500 pM to about 3 pM, from about 500 pM to about 2 pM, from about 500 pM to about 1 pM, or less than 1 pM. The dissociation constants (K_D) of anti-TREM2 antibodies for human TREM2 may range from about 250 pM to about 90 pM, from about 250 pM to about 80 pM, from about 250 pM to about 70 pM, from about 250 pM to about 60 pM, from about 250 pM to about 50 pM, from about 250 pM to about 40 pM, from about 250 pM to about 30 pM, from about 250 pM to about 20 pM, from about 250 pM to about 10 pM, from about 250 pM to about 9 pM, from about 250 pM to about 8 pM, from about 250 pM to about 7 pM, from about 250 pM to about 6 pM, from about 250 pM to about 5 pM, from about 250 pM to about 4 pM, from about 250

pM to about 3 pM, from about 250 pM to about 2 pM, from about 250 pM to about 1 pM, or less than 1 pM. The dissociation constants (K_D) of anti-TREM2 antibodies for human TREM2 may range from about 100 pM to about 90 pM, from about 100 pM to about 80 pM, from about 100 pM to about 70 pM, from about 100 pM to about 60 pM, from about 100 pM to about 50 pM, from about 100 pM to about 40 pM, from about 100 pM to about 30 pM, from about 100 pM to about 20 pM, from about 100 pM to about 10 pM, from about 100 pM to about 9 pM, from about 100 pM to about 8 pM, from about 100 pM to about 7 pM, from about 100 pM to about 6 pM, from about 100 pM to about 5 pM, from about 100 pM to about 4 pM, from about 100 pM to about 3 pM, from about 100 pM to about 2 pM, from about 100 pM to about 1 pM, or less than 1 pM. In some embodiments, the dissociation constant (K_D) is determined at a temperature of approximately 25°C. In some embodiments, the K_D is determined using a monovalent antibody (*e.g.*, a Fab) or a full-length antibody in a monovalent form. Methods for the preparation and selection of antibodies that interact and/or bind with specificity to TREM2 are described herein. (*e.g.*, see **Examples 1 and 2**).

[0234] In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for human TREM2 may be less than 260 nM, may be less than 225 nM, may be less than 200 nM, may be less than 150 nM, may be less than 135 nM, may be less than 125 nM, may be less than100 nM, may be less than 95 nM, may be less than 90 nM, may be less than 85 nM, may be less than 80 nM, may be less than 75 nM, may be less than 70 nM, may be less than 65 nM, may be less than 60 nM, may be less than 55 nM, may be less than 50 nM, may be less than 45 nM, may be less than 40 nM, may be less than 36 nM, may be less than 35 nM, may be less than 30 nM, may be less than 29 nM, may be less than 28 nM, may be less than 27 nM, may be less than 26 nM, may be less than 25 nM, may be less than 24 nM, may be less than 23 nM, may be less than 22 nM, may be less than 21 nM, may be less than 20 nM, may be less than 19 nM, may be less than 18.5 nM, may be less than 18 nM, may be less than 15 nM, may be less than 14 nM, may be less than 13 nM, may be less than 12 nM, may be less than 11 nM, may be less than 10 nM, may be less than 9.5 nM, may be less than 9 nM, may be less than 8.5 nM, may be less than 8 nM, may be less than 7.5 nM, may be less than 7 nM, may be less than 6.5 nM, may be less than 6 nM, may be less than 5.5 nM, may be less than 5 nM, may be less than 4.5 nM, may be less than 4 nM, may be less than 3.5 nM, may be less than 3 nM, may be less than 2.5 nM, may be less than 2 nM, may be less than 1.5 nM, may be less than 1 nM, may be less than 950 pM, may be less than 900 pM, may be less than 850 pM, may be less than 830 pM, may be less than 800 pM, may be less than 750 pM, may be less than 730 pM, may be less than 700 pM, may be less than 650 pM, may be less than 630 pM, may be less than 600 pM, may be less than 550 pM, may be less than 500 pM, may be less than 450 pM, may be less than 415 pM, may be less than 400 pM, may be less than 350 pM, may be less than 300 pM, may be less than 250 pM, may be less than 200 pM, may be less than 150 pM, may be less than 100 pM, may be less than 95 pM, may be less than 90 pM, may be less than 85 pM, may be less than 80 pM, may be less than 75pM, may be less than 70 pM, may be less than 65 pM, may be less than 60 pM, may be less than 55 pM, may be

less than 50 pM, may be less than 45 pM, may be less than 40 pM, may be less than 35 pM, may be less than 30 pM, may be less than 25 pM, may be less than 20 pM, may be less than 15 pM, may be less than 10 pM, may be less than 9 pM, may be less than 8 pM, may be less than 7 pM, may be less than 6 pM, may be less than 5 pM, may be less than 4 pM, may be less than 3 pM, may be less than 2 pM, or may be less than 1 pM. In some embodiments, the dissociation constant (K_D) is determined at a temperature of approximately 25°C. In some embodiments, the K_D is determined using a monovalent antibody (*e.g.*, a Fab) or a full-length antibody in a monovalent form. Methods for the preparation and selection of antibodies that interact and/or bind with specificity to TREM2 are described herein. (*e.g.*, see **Examples 1 and 2**).

[0235] In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 10 μM to about 100 pM, from about 200 nM to about 100 pM, from about 100 nM to about 100 pM, from about 90 nM to about 100 pM, from about 80 nM to about 100 pM, from about 70 nM to about 100 pM, from about 60 nM to about 100 pM, from about 50 nM to about 100 pM, from about 40 nM to about 100 pM, from about 30 nM to about 100 pM, from about 20 nM to about 100 pM, from about 10 nM to about 100 pM, from about 9 nM to about 100 pM, from about 8 nM to about 100 pM, from about 7 nM to about 100 pM, from about 6 nM to about 100 pM, from about 5 nM to about 100 pM, from about 4 nM to about 100 pM, from about 3 nM to about 100 pM, from about 2 nM to about 100 pM, from about 1 nM to about 100 pM, from 900 pM to about 100 pM, from about 800 pM to about 100 pM, from 700 pM to about 100 pM, from 600 pM to about 500 pM, from 400 pM to about 100 pM, from 300 pM to about 100 pM, from 200 pM to about 100 pM, from 900 pM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constant (K_D) is determined at a temperature of approximately 25°C. In some embodiments, the K_D is determined using a monovalent antibody (*e.g.*, a Fab) or a full-length antibody in a monovalent form. Methods for the preparation and selection of antibodies that interact and/or bind with specificity to TREM2 are described herein. (*e.g.*, see **Examples 1 and 2**).

[0236] In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 10 μM to about 900 pM, from about 10 μM to about 800 pM, from about 10 μM to about 700 pM, from about 10 μM to about 600 pM, from about 10 μM to about 500 pM, from about 10 μM to about 400 pM, from about 10 μM to about 300 pM, from about 10 μM to about 200 pM, from about 10 μM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 5 μM to about 900 pM, from about 5 μM to about 800 pM, from about 5 μM to about 700 pM, from about 5 μM to about 600 pM, from about 5 μM to about 500 pM, from about 5 μM to about 400 pM, from about 5 μM to about 300 pM, from about 5 μM to about 200 pM, from about 5 μM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 1 μM to about 900 pM, from about 1 μM to about 800 pM, from about 1 μM to about 700

pM, from about 1 μM to about 600 pM, from about 1 μM to about 500 pM, from about 1 μM to about 400 pM, from about 1 μM to about 300 pM, from about 1 μM to about 200 pM, from about 1 μM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 900 nM to about 900 pM, from about 900 nM to about 800 pM, from about 900 nM to about 700 pM, from about 900 nM to about 600 pM, from about 900 nM to about 500 pM, from about 900 nM to about 400 pM, from about 900 nM to about 300 pM, from about 900 nM to about 200 pM, from about 900 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 800 nM to about 900 pM, from about 800 nM to about 800 pM, from about 800 nM to about 700 pM, from about 800 nM to about 600 pM, from about 800 nM to about 500 pM, from about 800 nM to about 400 pM, from about 800 nM to about 300 pM, from about 800 nM to about 200 pM, from about 800 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 700 nM to about 900 pM, from about 700 nM to about 800 pM, from about 700 nM to about 700 pM, from about 700 nM to about 600 pM, from about 700 nM to about 500 pM, from about 700 nM to about 400 pM, from about 700 nM to about 300 pM, from about 700 nM to about 200 pM, from about 700 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 600 nM to about 900 pM, from about 600 nM to about 800 pM, from about 600 nM to about 700 pM, from about 600 nM to about 600 pM, from about 600 nM to about 500 pM, from about 600 nM to about 400 pM, from about 600 nM to about 300 pM, from about 600 nM to about 200 pM, from about 600 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 500 nM to about 900 pM, from about 500 nM to about 800 pM, from about 500 nM to about 700 pM, from about 500 nM to about 600 pM, from about 500 nM to about 500 pM, from about 500 nM to about 400 pM, from about 500 nM to about 300 pM, from about 500 nM to about 200 pM, from about 500 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 400 nM to about 900 pM, from about 400 nM to about 800 pM, from about 400 nM to about 700 pM, from about 400 nM to about 600 pM, from about 400 nM to about 500 pM, from about 400 nM to about 400 pM, from about 400 nM to about 300 pM, from about 400 nM to about 200 pM, from about 400 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 300 nM to about 900 pM, from about 300 nM to about 800 pM, from about 300 nM to about 700 pM, from about 300 nM to about 600 pM, from about 300 nM to about 500 pM, from about 300 nM to about 400 pM, from about 300 nM to about 300 pM, from about 300 nM to about 200 pM, from about 300 nM to about 100 pM, or less than 100 pM. In some

embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 200 nM to about 900 pM, from about 200 nM to about 800 pM, from about 200 nM to about 700 pM, from about 200 nM to about 600 pM, from about 200 nM to about 500 pM, from about 200 nM to about 400 pM, from about 200 nM to about 300 pM, from about 200 nM to about 200 pM, from about 200 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 100 nM to about 900 pM, from about 100 nM to about 800 pM, from about 100 nM to about 700 pM, from about 100 nM to about 600 pM, from about 100 nM to about 500 pM, from about 100 nM to about 400 pM, from about 100 nM to about 300 pM, from about 100 nM to about 200 pM, from about 100 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 90 nM to about 900 pM, from about 90 nM to about 800 pM, from about 90 nM to about 700 pM, from about 90 nM to about 600 pM, from about 90 nM to about 500 pM, from about 90 nM to about 400 pM, from about 90 nM to about 300 pM, from about 90 nM to about 200 pM, from about 90 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 80 nM to about 900 pM, from about 80 nM to about 800 pM, from about 80 nM to about 700 pM, from about 80 nM to about 600 pM, from about 80 nM to about 500 pM, from about 80 nM to about 400 pM, from about 80 nM to about 300 pM, from about 80 nM to about 200 pM, from about 80 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 70 nM to about 900 pM, from about 70 nM to about 800 pM, from about 70 nM to about 700 pM, from about 70 nM to about 600 pM, from about 70 nM to about 500 pM, from about 70 nM to about 400 pM, from about 70 nM to about 300 pM, from about 70 nM to about 200 pM, from about 70 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 60 nM to about 900 pM, from about 60 nM to about 800 pM, from about 60 nM to about 700 pM, from about 60 nM to about 600 pM, from about 60 nM to about 500 pM, from about 60 nM to about 400 pM, from about 60 nM to about 300 pM, from about 60 nM to about 200 pM, from about 60 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 50 nM to about 900 pM, from about 50 nM to about 800 pM, from about 50 nM to about 700 pM, from about 50 nM to about 600 pM, from about 50 nM to about 500 pM, from about 50 nM to about 400 pM, from about 50 nM to about 300 pM, from about 50 nM to about 200 pM, from about 50 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 40 nM to about 900 pM, from about 40 nM to about 800 pM, from about 40 nM to about 700 pM, from about 40 nM to about 600 pM, from about 40 nM to about 500 pM, from about 40 nM

to about 400 pM, from about 40 nM to about 300 pM, from about 40 nM to about 200 pM, from about 40 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 30 nM to about 900 pM, from about 30 nM to about 800 pM, from about 30 nM to about 700 pM, from about 30 nM to about 600 pM, from about 30 nM to about 500 pM, from about 30 nM to about 400 pM, from about 30 nM to about 300 pM, from about 30 nM to about 200 pM, from about 30 nM to about 100 pM, or less than 100 pM, from about 20 nM to about 900 pM, from about 20 nM to about 800 pM, from about 20 nM to about 700 pM, from about 20 nM to about 600 pM, from about 20 nM to about 500 pM, from about 20 nM to about 400 pM, from about 20 nM to about 300 pM, from about 20 nM to about 200 pM, from about 20 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 10 nM to about 900 pM, from about 10 nM to about 800 pM, from about 10 nM to about 700 pM, from about 10 nM to about 600 pM, from about 10 nM to about 500 pM, from about 10 nM to about 400 pM, from about 10 nM to about 300 pM, from about 10 nM to about 200 pM, from about 10 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 9 nM to about 900 pM, from about 9 nM to about 800 pM, from about 9 nM to about 700 pM, from about 9 nM to about 600 pM, from about 9 nM to about 500 pM, from about 9 nM to about 400 pM, from about 9 nM to about 300 pM, from about 9 nM to about 200 pM, from about 9 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 8 nM to about 900 pM, from about 8 nM to about 800 pM, from about 8 nM to about 700 pM, from about 8 nM to about 600 pM, from about 8 nM to about 500 pM, from about 8 nM to about 400 pM, from about 8 nM to about 300 pM, from about 8 nM to about 200 pM, from about 8 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 7 nM to about 900 pM, from about 7 nM to about 800 pM, from about 7 nM to about 700 pM, from about 7 nM to about 600 pM, from about 7 nM to about 500 pM, from about 7 nM to about 400 pM, from about 7 nM to about 300 pM, from about 7 nM to about 200 pM, from about 7 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 6 nM to about 900 pM, from about 6 nM to about 800 pM, from about 6 nM to about 700 pM, from about 6 nM to about 600 pM, from about 6 nM to about 500 pM, from about 6 nM to about 400 pM, from about 6 nM to about 300 pM, from about 6 nM to about 200 pM, from about 6 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 5 nM to about 900 pM, from about 5 nM to about 800 pM, from about 5 nM to about 700 pM, from about 5 nM to about 600 pM, from about 5 nM to about 500 pM, from about 5 nM to about 400 pM, from about 5 nM to about 300 pM, from about 5 nM to about

200 pM, from about 5 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 4 nM to about 900 pM, from about 4 nM to about 800 pM, from about 4 nM to about 700 pM, from about 4 nM to about 600 pM, from about 4 nM to about 500 pM, from about 4 nM to about 400 pM, from about 4 nM to about 300 pM, from about 4 nM to about 200 pM, from about 4 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 3 nM to about 900 pM, from about 3 nM to about 800 pM, from about 3 nM to about 700 pM, from about 3 nM to about 600 pM, from about 3 nM to about 500 pM, from about 3 nM to about 400 pM, from about 3 nM to about 300 pM, from about 3 nM to about 200 pM, from about 3 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 2 nM to about 900 pM, from about 2 nM to about 800 pM, from about 2 nM to about 700 pM, from about 2 nM to about 600 pM, from about 2 nM to about 500 pM, from about 2 nM to about 400 pM, from about 2 nM to about 300 pM, from about 2 nM to about 200 pM, from about 2 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may range from about 1 nM to about 900 pM, from about 1 nM to about 800 pM, from about 1 nM to about 700 pM, from about 1 nM to about 600 pM, from about 1 nM to about 500 pM, from about 1 nM to about 400 pM, from about 1 nM to about 300 pM, from about 1 nM to about 200 pM, from about 1 nM to about 100 pM, or less than 100 pM. In some embodiments, the dissociation constant (K_D) is determined at a temperature of approximately 25°C. In some embodiments, the K_D is determined using a monovalent antibody (*e.g.*, a Fab) or a full-length antibody in a monovalent form. Methods for the preparation and selection of antibodies that interact and/or bind with specificity to TREM2 are described herein. (*e.g.*, see **Examples 1 and 2**).

[0237] In some embodiments, the dissociation constants (K_D) of anti-TREM2 antibodies for cynomolgus monkey TREM2 may be less than 6 μM, may be less than 5 μM, may be less than 4.6 μM, may be less than 4 μM, may be less than 3 μM, may be less than 2 μM, may be less than 1.5 μM, may be less than 1 μM, may be less than 900 nM, may be less than 800 nM, may be less than 700 nM, may be less than 600 nM, may be less than 500 nM, may be less than 400 nM, may be less than 300 nM, may be less than 200 nM, may be less than100 nM, may be less than 95 nM, may be less than 90 nM, may be less than 85 nM, may be less than 80 nM, may be less than 75 nM, may be less than 70 nM, may be less than 65 nM, may be less than 60 nM, may be less than 55 nM, may be less than 50 nM, may be less than 45 nM, may be less than 40 nM, may be less than 36 nM, may be less than 35 nM, may be less than 31 nM, may be less than 30 nM, may be less than 29 nM, may be less than 28 nM, may be less than 27 nM, may be less than 26 nM, may be less than 25 nM, may be less than 24 nM, may be less than 23 nM, may be less than 22 nM, may be less than 21 nM, may be less than 20 nM, may be less than 19 nM, may be less than 18.5 nM, may be less than 18 nM, may be less than,

may be 17 nM, may be than 16.5 nM, may be less than 16 nM, may be less than 15.5 nM, may be less than 15 nM, may be less than 14.5 nM, may be less than 14 nM, may be less than 13 nM, may be less than 12 nM, may be less than 11 nM, may be less than 10 nM, may be less than 9.5 nM, may be less than 9 nM, may be less than 8.5 nM, may be less than 8 nM, may be less than 7.5 nM, may be less than 7 nM, may be less than 6.5 nM, may be less than 6 nM, may be less than 5.5 nM, may be less than 5 nM, may be less than 4.5 nM, may be less than 4 nM, may be less than 3.5 nM, may be less than 3 nM, may be less than 2.5 nM, may be less than 2 nM, may be less than 1.5 nM, may be less than 1 nM, may be less than 950 pM, may be less than 900 pM, may be less than 890 pM, may be less than 850 pM, may be less than 800 pM, may be less than 750 pM, may be less than 700 pM, may be less than 650 pM, may be less than 600 pM, may be less than 550 pM, may be less than 500 pM, may be less than 450 pM, may be less than 400 pM, may be less than 375 pM, may be less than 350 pM, may be less than 325 pM, may be less than 300 pM, may be less than 270 pM, may be less than 250 pM, may be less than 225 pM, may be less than 200 pM, may be less than 150 pM, or may be less than 100 pM. In some embodiments, the dissociation constant (K_D) is determined at a temperature of approximately 25°C. In some embodiments, the K_D is determined using a monovalent antibody (*e.g.*, a Fab) or a full-length antibody in a monovalent form. Methods for the preparation and selection of antibodies that interact and/or bind with specificity to TREM2 are described herein. (*e.g.*, see **Examples 1 and 2**).

[0238] Dissociation constants may be determined through any analytical technique, including any biochemical or biophysical technique such as ELISA, surface plasmon resonance (SPR), bio-layer interferometry (*see, e.g.*, Octet System by ForteBio), isothermal titration calorimetry (ITC), differential scanning calorimetry (DSC), circular dichroism (CD), stopped-flow analysis, and colorimetric or fluorescent protein melting analyses. In some embodiments, the dissociation constant (K_D) for TREM2 is determined at a temperature of approximately25°C. In some embodiments, the K_D is determined using a monovalent antibody (*e.g.*, a Fab) or a full-length antibody. In some embodiments, the K_D is determined using a full-length antibody in a monovalent form. Utilizing, for example, any assay described herein (see, *e.g.*, **Examples 1 and 2**).

[0239] Additional anti-TREM2 antibodies, *e.g.*, antibodies that specifically bind to a TREM2 protein of the present disclosure, may be identified, screened, and/or characterized for their physical/chemical properties and/or biological activities by various assays known in the art.

Bispecific antibodies

[0240] Certain aspects of the present disclosure relate to bispecific antibodies that bind to a TREM2 protein of the present disclosure and a second antigen. Methods of generating bispecific antibodies are well known in the art and described herein. In some embodiments, bispecific antibodies of the present disclosure bind to one or more amino acid residues of human TREM2 (SEQ ID NO: 1), or amino acid residues on a TREM2 protein corresponding to amino acid residues of SEQ ID NO: 1.

In other embodiments, bispecific antibodies of the present disclosure also bind to one or more amino acid residues of human DAP12.

[0241] In some embodiments, bispecific antibodies of the present disclosure recognize a first antigen and a second antigen. In some embodiments, the first antigen is human TREM2 or a naturally occurring variant thereof, or human DAP12 or a naturally occurring variant thereof. In some embodiments, 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 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 angiopep peptide, and ANG1005; (c) a disease-causing protein selected from 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; and (d) ligands and/or proteins expressed on immune cells, wherein the ligands and/or proteins selected from 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 and any combination thereof.

Antibody fragments

[0242] Certain aspects of the present disclosure relate to antibody fragments that bind to one or more of human TREM2, a naturally occurring variant of human TREM2, and a disease variant of human TREM2. In some embodiments, the antibody fragment is an Fab, Fab', Fab'-SH, F(ab')2, Fv or scFv fragment. In some embodiments, the antibody fragment is used in combination with one or more antibodies that specifically bind a disease-causing protein selected from: a) an antigen facilitating transport across the blood-brain-barrier; (b) an antigen facilitating transport across the blood-brain-barrier selected from 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 angiopep peptide, and ANG1005; (c) a disease-causing protein selected from 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; and (d) ligands and/or proteins expressed on immune cells, wherein the ligands and/or proteins selected from 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 , and any combination thereof.

Antibody frameworks

[0243] Any of the antibodies described herein further include a framework. In some embodiments, the framework is a human immunoglobulin framework. For example, in some embodiments, an antibody (*e.g.,* an anti-TREM2 antibody) comprises HVRs as in any of the above embodiments and further comprises an acceptor human framework, *e.g.*, a human immunoglobulin framework or a human consensus framework. Human immunoglobulin frameworks may be part of the human antibody, or a non-human antibody may be humanized by replacing one or more endogenous frameworks with human framework region(s). Human framework regions that may be used for humanization include but are not limited to: framework regions selected using the "best-fit" method (see, *e.g.*, Sims et al. *J. Immunol.* 151:2296 (1993)); framework regions derived from the consensus sequence of human antibodies of a particular subgroup of light or heavy chain variable regions (see, *e.g.*, Carter et al. *Proc. Natl. Acad. Sci. USA*, 89:4285 (1992); and Presta et al. *J. Immunol.*, 151:2623 (1993)); human mature (somatically mutated) framework regions or human germline framework regions (see, *e.g.*, Almagro and Fransson, *Front. Biosci.* 13:1619-1633 (2008)); and framework regions derived from screening FR libraries (see, *e.g.*, Baca et al., *J. Biol. Chem.* 272:10678-10684 (1997) and Rosok et al., *J. Biol. Chem.* 271:22611-22618 (1996)).

[0244] In some embodiments, an antibody comprises a heavy chain variable region comprising an HVR-H1, an HVR-H2, and an HVR-H3 of the present disclosure and one, two, three or four of the heavy chain framework regions as shown in **Tables 4A to 4D**. In some embodiments, an antibody comprises a light chain variable region comprising an HVR-L1, an HVR-L2, and an HVR-L3 of the present disclosure and one, two, three or four of the light chain framework regions as shown in **Tables 5A to 5D**. In some embodiments, an antibody comprises a heavy chain variable region comprising an HVR-H1, an HVR-H2, and an HVR-H3 of the present disclosure and one, two, three or four of the heavy chain framework regions as shown in **Tables 4A to 4D** and further comprises a light chain

variable region comprising an HVR-L1, an HVR-L2, and an HVR-L3 of the present disclosure and one, two, three or four of the light chain framework regions as shown in **Tables 5A to 5D**.

Modulated expression of pro-inflammatory mediators

[0245] In some embodiments, the anti-TREM2 antibodies of the present disclosure may modulate (*e.g.*, increase or decrease) the expression of pro-inflammatory mediators after binding to a TREM2 protein expressed in a cell.

[0246] As used herein, pro-inflammatory mediators are proteins involved either directly or indirectly (*e.g.*, by way of pro-inflammatory signaling pathways) in a mechanism that induces, activates, promotes, or otherwise increases an inflammatory response. Any method known in the art for identifying and characterizing pro-inflammatory mediators may be used. Examples of pro-inflammatory mediators include, without limitation, cytokines such as IFN-β, IL-1α, IL-1β, TNF-α, IL-6, IL-8, CRP, CD86, MCP-1/CCL2, CCL3, CCL4, CCL5, CCR2, CXCL-10, Gata3, IL-20 family members, IL-33, LIF, IFN-gamma, OSM, CNTF, CSF-1, OPN, CD11c, GM-CSF, IL-11, IL-12, IL-17, IL-18, and IL-23.

[0247] In some embodiments, the anti-TREM2 antibodies of the present disclosure may modulate functional expression and/or secretion of pro-inflammatory mediators, such as FN-β, IL-1α, IL-1β, CD86, TNF-α, IL-6, IL-8, CRP, MCP-1/CCL2, CCL3, CCL4, CCL5, CCR2, CXCL-10, Gata3, IL-20 family members, IL-33, LIF, IFN-gamma, OSM, CNTF, CSF1, OPN, CD11c, GM-CSF, IL-11, IL-12, IL-17, IL-18, and IL-23. In certain embodiments, modulated expression of the pro-inflammatory mediators occurs in macrophages, dendritic cells, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or microglial cells. Modulated expression may include, without limitation, modulated gene expression, modulated transcriptional expression, or modulated protein expression. Any method known in the art for determining gene, transcript (*e.g.*, mRNA), and/or protein expression may be used. For example, Northern blot analysis may be used to determine pro-inflammatory mediator gene expression levels, RT-PCR may be used to determine the level of pro-inflammatory mediator transcription, and Western blot analysis may be used to determine pro-inflammatory mediator protein levels.

[0248] In certain embodiments, pro-inflammatory mediators include inflammatory cytokines. Accordingly, in certain embodiments, the anti-TREM2 antibodies of the present disclosure may modulate secretion of one or more inflammatory cytokines. Examples of inflammatory cytokines whose secretion may be reduced by the anti-TREM2 antibodies of the present disclosure include, without limitation, FN-β, IL-1α, IL-1β, CD86, TNF-α, IL-6, IL-8, CRP, MCP-1/CCL2, CCL3, CCL4, CCL5, CCR2, CXCL-10, Gata3, IL-20 family members, IL-33, LIF, IFN-gamma, OSM, CNTF, CSF1, OPN, CD11c, GM-CSF, IL-11, IL-12, IL-17, IL-18, and IL-23.

[0249] In certain embodiments, pro-inflammatory mediators include inflammatory receptors. Accordingly, in certain embodiments, the anti-TREM2 antibodies of the present disclosure may

modulate expression of one or more inflammatory receptors. Examples of inflammatory receptors whose expression may be reduced by the anti-TREM2 antibodies of the present disclosure include, without limitation, CD86.

[0250] As used herein, a pro-inflammatory mediator may have modulated expression if its expression in one or more cells of a subject treated with an anti-TREM2 antibody of the present disclosure is modulated (*e.g.*, increased or decreased) as compared to the expression of the same pro-inflammatory mediator expressed in one or more cells of a corresponding subject that is not treated with the anti-TREM2 antibody. In some embodiments, the anti-TREM2 antibody of the present disclosure may modulate pro-inflammatory mediator expression in one or more cells of a subject by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 160%, at least 170%, at least 180%, at least 190%, or at least 200% for example, as compared to pro-inflammatory mediator expression in one or more cells of a corresponding subject that is not treated with the anti-TREM2 antibody. In other embodiments, the anti-TREM2 antibody may modulate pro-inflammatory mediator expression in one or more cells of a subject by at least 1.5 fold, at least 1.6 fold, at least 1.7 fold, at least 1.8 fold, at least 1.9 fold, at least 2.0 fold, at least 2.1 fold, at least 2.15 fold, at least 2.2 fold, at least 2.25 fold, at least 2.3 fold, at least 2.35 fold, at least 2.4 fold, at least 2.45 fold, at least 2.5 fold, at least 2.55 fold, at least 3.0 fold, at least 3.5 fold, at least 4.0 fold, at least 4.5 fold, at least 5.0 fold, at least 5.5 fold, at least 6.0 fold, at least 6.5 fold, at least 7.0 fold, at least 7.5 fold, at least 8.0 fold, at least 8.5 fold, at least 9.0 fold, at least 9.5 fold, or at least 10 fold, for example, as compared to pro-inflammatory mediator expression in one or more cells of a corresponding subject that is not treated with the anti-TREM2 antibody.

[0251] In some embodiments, anti-TREM2 antibodies of the present disclosure may be useful for preventing, lowering the risk of, or treating conditions and/or diseases associated with abnormal levels of one or more pro-inflammatory mediators, including dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, tauopathy disease, Nasu-Hakola disease, stroke, acute trauma, chronic trauma, cognitive deficit, memory loss, lupus, acute and chronic colitis, rheumatoid arthritis, wound healing, Crohn's disease, inflammatory bowel disease, ulcerative colitis, obesity, malaria, essential tremor, central nervous system lupus, Behcet's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, Shy-Drager syndrome, progressive supranuclear palsy, cortical basal ganglionic degeneration, acute disseminated encephalomyelitis, granulomartous disorders, sarcoidosis, diseases of aging, seizures, spinal cord injury, traumatic brain injury, age related macular degeneration, glaucoma, retinitis pigmentosa, retinal degeneration, respiratory tract infection, sepsis, eye infection, systemic infection, lupus, arthritis, multiple sclerosis,

low bone density, osteoporosis, osteogenesis, osteopetrotic disease, Paget's disease of bone, cancer, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, polycythemia vera, essential thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express TREM2, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza, comprising administering to an individual in need thereof a therapeutically effective amount of an agent that does not inhibit interaction between TREM2 and one or more TREM2 ligands, and/or enhance one or more activities of at least one TREM2 ligand,. Other aspects of the present disclosure relate to an agent that does not inhibit interaction between TREM2 and one or more TREM2 ligands, and/or enhance one or more activities of at least one TREM2 ligand, for use in preventing, reducing risk, or treating a disease, disorder, or injury selected from dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, tauopathy disease, Nasu-Hakola disease, stroke, acute trauma, chronic trauma, cognitive deficit, memory loss, lupus, acute and chronic colitis, rheumatoid arthritis, wound healing, Crohn's disease, inflammatory bowel disease, ulcerative colitis, obesity, malaria, essential tremor, central nervous system lupus, Behcet's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, Shy-Drager syndrome, progressive supranuclear palsy, cortical basal ganglionic degeneration, acute disseminated encephalomyelitis, granulomartous disorders, sarcoidosis, diseases of aging, seizures, spinal cord injury, traumatic brain injury, age related macular degeneration, glaucoma, retinitis pigmentosa, retinal degeneration, respiratory tract infection, sepsis, eye infection, systemic infection, lupus, arthritis, multiple sclerosis, low bone density, osteoporosis, osteogenesis, osteopetrotic disease, Paget's disease of bone, cancer, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, polycythemia vera, essential thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express TREM2, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection,

Campylobacter jejuni infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza.

Syk phosphorylation

[0252] In some embodiments, the anti-TREM2 antibodies of the present disclosure may induce spleen tyrosine kinase (Syk) phosphorylation after binding to a TREM2 protein expressed in a cell.

[0253] Spleen tyrosine kinase (Syk) is an intracellular signaling molecule that functions downstream of TREM2 by phosphorylating several substrates, thereby facilitating the formation of a signaling complex leading to cellular activation and inflammatory processes.

[0254] In some embodiments, anti-TREM2 antibodies of the present disclosure may be beneficial for preventing, lowering the risk of, or treating conditions and/or diseases associated with decreased levels of Syk phosphorylation, including dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, tauopathy disease, Nasu-Hakola disease, stroke, acute trauma, chronic trauma, cognitive deficit, memory loss, lupus, acute and chronic colitis, rheumatoid arthritis, wound healing, Crohn's disease, inflammatory bowel disease, ulcerative colitis, obesity, malaria, essential tremor, central nervous system lupus, Behcet's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, Shy-Drager syndrome, progressive supranuclear palsy, cortical basal ganglionic degeneration, acute disseminated encephalomyelitis, granulomartous disorders, sarcoidosis, diseases of aging, seizures, spinal cord injury, traumatic brain injury, age related macular degeneration, glaucoma, retinitis pigmentosa, retinal degeneration, respiratory tract infection, sepsis, eye infection, systemic infection, lupus, arthritis, multiple sclerosis, low bone density, osteoporosis, osteogenesis, osteopetrotic disease, Paget's disease of bone, cancer, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, polycythemia vera, essential thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express TREM2, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza, comprising administering to an individual in need thereof a therapeutically effective amount of an agent that does not inhibit interaction between TREM2 and one or more TREM2 ligands, and/or enhance one or more activities of at least one TREM2 ligand,. Other aspects of the present disclosure relate to an agent that does not inhibit interaction between TREM2 and one or more TREM2 ligands, and/or enhance one or more activities of at least one TREM2

ligand, for use in preventing, reducing risk, or treating a disease, disorder, or injury selected from dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, tauopathy disease, Nasu-Hakola disease, stroke, acute trauma, chronic trauma, cognitive deficit, memory loss, lupus, acute and chronic colitis, rheumatoid arthritis, wound healing, Crohn's disease, inflammatory bowel disease, ulcerative colitis, obesity, malaria, essential tremor, central nervous system lupus, Behcet's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, Shy-Drager syndrome, progressive supranuclear palsy, cortical basal ganglionic degeneration, acute disseminated encephalomyelitis, granulomartous disorders, sarcoidosis, diseases of aging, seizures, spinal cord injury, traumatic brain injury, age related macular degeneration, glaucoma, retinitis pigmentosa, retinal degeneration, respiratory tract infection, sepsis, eye infection, systemic infection, lupus, arthritis, multiple sclerosis, low bone density, osteoporosis, osteogenesis, osteopetrotic disease, Paget's disease of bone, cancer, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, polycythemia vera, essential thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express TREM2, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza..

DAP12 binding and phosphorylation

[0255] In some embodiments, the anti-TREM2 antibodies of the present disclosure may induce binding of TREM2 to DAP12. In other embodiments, the anti-TREM2 antibodies of the present disclosure may induce DAP12 phosphorylation after binding to a TREM2 protein expressed in a cell. In other embodiments, TREM2-mediated DAP12 phosphorylation is induced by one or more SRC family tyrosine kinases. Examples of Src family tyrosine kinases include, without limitation, Src, Syk, Yes, Fyn, Fgr, Lck, Hck, Blk, Lyn, and Frk.

[0256] DAP12 is variously referred to as TYRO protein tyrosine kinase-binding protein, TYROBP, KARAP, and PLOSL. DAP12 is a transmembrane signaling protein that contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain. In certain embodiments, the anti-TREM2 antibody may induce DAP12 phosphorylation in its ITAM motif. Any method known in the art for determining protein phosphorylation, such as DAP12 phosphorylation, may be used.

[0257] In some embodiments, DAP12 is phosphorylated by SRC family kinases, resulting in the recruitment and activation of the Syk kinase, ZAP70 kinase, or both, to a DAP12/TREM2 complex. Thus, in certain embodiments, the anti-TREM2 antibodies of the present disclosure may recruit Syk, ZAP70, or both to a DAP12/TREM2 complex. Without wishing to be bound by theory, it is believed that anti-TREM2 a antibodies of the present disclosure are useful for preventing, lowering the risk of, or treating conditions and/or diseases associated with decreased levels of DAP12 activity, DAP12 phosphorylation, or recruitment of Syk, ZAP70, or both to a DAP12/TREM2 complex, including dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, tauopathy disease, Nasu-Hakola disease, stroke, acute trauma, chronic trauma, cognitive deficit, memory loss, lupus, acute and chronic colitis, rheumatoid arthritis, wound healing, Crohn's disease, inflammatory bowel disease, ulcerative colitis, obesity, malaria, essential tremor, central nervous system lupus, Behcet's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, Shy-Drager syndrome, progressive supranuclear palsy, cortical basal ganglionic degeneration, acute disseminated encephalomyelitis, granulomartous disorders, sarcoidosis, diseases of aging, seizures, spinal cord injury, traumatic brain injury, age related macular degeneration, glaucoma, retinitis pigmentosa, retinal degeneration, respiratory tract infection, sepsis, eye infection, systemic infection, lupus, arthritis, multiple sclerosis, low bone density, osteoporosis, osteogenesis, osteopetrotic disease, Paget's disease of bone, cancer, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, polycythemia vera, essential thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express TREM2, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza, comprising administering to an individual in need thereof a therapeutically effective amount of an agent that does not inhibit interaction between TREM2 and one or more TREM2 ligands, and/or enhance one or more activities of one or more TREM2 ligands, Other aspects of the present disclosure relate to an agent does not inhibit interaction between TREM2 and one or more TREM2 ligands, and/or enhance one or more activities of one or more TREM2 ligands, use in preventing, reducing risk, or treating a disease, disorder, or injury selected from dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, tauopathy disease, Nasu-Hakola disease, stroke, acute trauma, chronic trauma, cognitive deficit,

memory loss, lupus, acute and chronic colitis, rheumatoid arthritis, wound healing, Crohn's disease, inflammatory bowel disease, ulcerative colitis, obesity, malaria, essential tremor, central nervous system lupus, Behcet's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, Shy-Drager syndrome, progressive supranuclear palsy, cortical basal ganglionic degeneration, acute disseminated encephalomyelitis, granulomartous disorders, sarcoidosis, diseases of aging, seizures, spinal cord injury, traumatic brain injury, age related macular degeneration, glaucoma, retinitis pigmentosa, retinal degeneration, respiratory tract infection, sepsis, eye infection, systemic infection, lupus, arthritis, multiple sclerosis, low bone density, osteoporosis, osteogenesis, osteopetrotic disease, Paget's disease of bone, cancer, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, polycythemia vera, essential thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express TREM2, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza.

Proliferation, survival and functionality of TREM2-expressing cells

[0258] In some embodiments, the anti-TREM2 antibodies of the present disclosure may increase the proliferation, survival, and/or function of dendritic cells, macrophages, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, and microglial cells (microglia) after binding to TREM2 protein expressed in a cell. In some embodiments, the anti-TREM2 antibodies of the present disclosure do not inhibit the growth (*e.g.*, proliferation and/or survival) of one or more innate immune cells.

[0259] Microglial cells are a type of glial cell that are the resident macrophages of the brain and spinal cord, and thus act as the first and main form of active immune defense in the central nervous system (CNS). Microglial cells constitute 20% of the total glial cell population within the brain. Microglial cells are constantly scavenging the CNS for plaques, damaged neurons and infectious agents. The brain and spinal cord are considered "immune privileged" organs in that they are separated from the rest of the body by a series of endothelial cells known as the blood–brain barrier, which prevents most infections from reaching the vulnerable nervous tissue. In the case where infectious agents are directly introduced to the brain or cross the blood–brain barrier, microglial cells must react quickly to decrease inflammation and destroy the infectious agents before they damage the sensitive neural tissue. Due to the unavailability of antibodies from the rest of the body (few

antibodies are small enough to cross the blood brain barrier), microglia must be able to recognize foreign bodies, swallow them, and act as antigen-presenting cells activating T-cells. Since this process must be done quickly to prevent potentially fatal damage, microglial cells are extremely sensitive to even small pathological changes in the CNS. They achieve this sensitivity in part by having unique potassium channels that respond to even small changes in extracellular potassium.

[0260] As used herein, macrophages of the present disclosure include, without limitation, M1 macrophages, activated M1 macrophages, and M2 macrophages. As used herein, microglial cells of the present disclosure include, without limitation, M1 microglial cells, activated M1 microglial cells, and M2 microglial cells. In some embodiments, anti-TREM2 antibodies of the present disclosure may be beneficial for, lowering the risk of, or treating conditions and/or diseases associated with decreased proliferation or survival, of immune cells, including dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, tauopathy disease, Nasu-Hakola disease, stroke, acute trauma, chronic trauma, cognitive deficit, memory loss, lupus, acute and chronic colitis, rheumatoid arthritis, wound healing, Crohn's disease, inflammatory bowel disease, ulcerative colitis, obesity, malaria, essential tremor, central nervous system lupus, Behcet's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, Shy-Drager syndrome, progressive supranuclear palsy, cortical basal ganglionic degeneration, acute disseminated encephalomyelitis, granulomartous disorders, sarcoidosis, diseases of aging, seizures, spinal cord injury, traumatic brain injury, age related macular degeneration, glaucoma, retinitis pigmentosa, retinal degeneration, respiratory tract infection, sepsis, eye infection, systemic infection, lupus, arthritis, multiple sclerosis, low bone density, osteoporosis, osteogenesis, osteopetrotic disease, Paget's disease of bone, cancer, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, polycythemia vera, essential thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express TREM2, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza, comprising administering to an individual in need thereof a therapeutically effective amount of an agent that does not inhibit interaction between TREM2 and one or more TREM2 ligands, and/or enhance one or more activities of one or more TREM2 ligands. Other aspects of the present disclosure relate to an agent that does not inhibit interaction between TREM2 and one or more TREM2 ligands, and/or enhance one or more activities of one or more TREM2 ligands for use in preventing, reducing risk, or treating a disease, disorder, or injury selected from

dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, tauopathy disease, Nasu-Hakola disease, stroke, acute trauma, chronic trauma, cognitive deficit, memory loss, lupus, acute and chronic colitis, rheumatoid arthritis, wound healing, Crohn's disease, inflammatory bowel disease, ulcerative colitis, obesity, malaria, essential tremor, central nervous system lupus, Behcet's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, Shy-Drager syndrome, progressive supranuclear palsy, cortical basal ganglionic degeneration, acute disseminated encephalomyelitis, granulomartous disorders, sarcoidosis, diseases of aging, seizures, spinal cord injury, traumatic brain injury, age related macular degeneration, glaucoma, retinitis pigmentosa, retinal degeneration, respiratory tract infection, sepsis, eye infection, systemic infection, lupus, arthritis, multiple sclerosis, low bone density, osteoporosis, osteogenesis, osteopetrotic disease, Paget's disease of bone, cancer, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, polycythemia vera, essential thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express TREM2, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza.

[0261] In some embodiments, anti-TREM2 antibodies of the present disclosure may increase the expression of CD83 and/or CD86 on dendritic cells, monocytes, and/or macrophages.

[0262] As used herein, the rate of proliferation, survival, and/or function of macrophages, dendritic cells, monocytes, and/or microglia may include increased expression if the rate of proliferation, survival, and/or function of dendritic cells, macrophages, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or microglia in a subject treated with an anti-TREM2 antibody of the present disclosure is greater than the rate of proliferation, survival, and/or function of dendritic cells, macrophages, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or microglia in a corresponding subject that is not treated with the anti-TREM2 antibody. In some embodiments, an anti-TREM2 antibody of the present disclosure may increase the rate of proliferation, survival, and/or function of dendritic cells, macrophages, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or microglia in a subject by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at

least 135%, at least 140%, at least 145%, at least 150%, at least 160%, at least 170%, at least 180%, at least 190%, or at least 200% for example, as compared to the rate of proliferation, survival, and/or function of dendritic cells, macrophages, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or microglia in a corresponding subject that is not treated with the anti-TREM2 antibody. In other embodiments, an anti-TREM2 antibody of the present disclosure may increase the rate of proliferation, survival, and/or function of dendritic cells, macrophages, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or microglia in a subject by at least 1.5 fold, at least 1.6 fold, at least 1.7 fold, at least 1.8 fold, at least 1.9 fold, at least 2.0 fold, at least 2.1 fold, at least 2.15 fold, at least 2.2 fold, at least 2.25 fold, at least 2.3 fold, at least 2.35 fold, at least 2.4 fold, at least 2.45 fold, at least 2.5 fold, at least 2.55 fold, at least 3.0 fold, at least 3.5 fold, at least 4.0 fold, at least 4.5 fold, at least 5.0 fold, at least 5.5 fold, at least 6.0 fold, at least 6.5 fold, at least 7.0 fold, at least 7.5 fold, at least 8.0 fold, at least 8.5 fold, at least 9.0 fold, at least 9.5 fold, or at least 10 fold, for example, as compared to the rate of proliferation, survival, and/or function of dendritic cells, macrophages, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or microglia in a corresponding subject that is not treated with the anti-TREM2 antibody.

[0263] In some embodiments, anti-TREM2 antibodies of the present disclosure may be beneficial for preventing, lowering the risk of, or treating conditions and/or diseases associated with a reduction in function of dendritic cells, macrophages, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, and/or microglia including dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, tauopathy disease, Nasu-Hakola disease, stroke, acute trauma, chronic trauma, cognitive deficit, memory loss, lupus, acute and chronic colitis, rheumatoid arthritis, wound healing, Crohn's disease, inflammatory bowel disease, ulcerative colitis, obesity, malaria, essential tremor, central nervous system lupus, Behcet's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, Shy-Drager syndrome, progressive supranuclear palsy, cortical basal ganglionic degeneration, acute disseminated encephalomyelitis, granulomartous disorders, sarcoidosis, diseases of aging, seizures, spinal cord injury, traumatic brain injury, age related macular degeneration, glaucoma, retinitis pigmentosa, retinal degeneration, respiratory tract infection, sepsis, eye infection, systemic infection, lupus, arthritis, multiple sclerosis, low bone density, osteoporosis, osteogenesis, osteopetrotic disease, Paget's disease of bone, cancer, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, polycythemia vera, essential thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express TREM2, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome

infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza, comprising administering to an individual in need thereof a therapeutically effective amount of an agent that does not inhibit interaction between TREM2 and one or more TREM2 ligands, and/or enhance one or more activities of at least one TREM2 ligand. Other aspects of the present disclosure relate to an agent that does not inhibit interaction between TREM2 and one or more TREM2 ligands, and/or enhance one or more activities of at least one TREM2 ligand for use in preventing, reducing risk, or treating a disease, disorder, or injury selected from dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, tauopathy disease, Nasu-Hakola disease, stroke, acute trauma, chronic trauma, cognitive deficit, memory loss, lupus, acute and chronic colitis, rheumatoid arthritis, wound healing, Crohn's disease, inflammatory bowel disease, ulcerative colitis, obesity, malaria, essential tremor, central nervous system lupus, Behcet's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, Shy-Drager syndrome, progressive supranuclear palsy, cortical basal ganglionic degeneration, acute disseminated encephalomyelitis, granulomartous disorders, sarcoidosis, diseases of aging, seizures, spinal cord injury, traumatic brain injury, age related macular degeneration, glaucoma, retinitis pigmentosa, retinal degeneration, respiratory tract infection, sepsis, eye infection, systemic infection, lupus, arthritis, multiple sclerosis, low bone density, osteoporosis, osteogenesis, osteopetrotic disease, Paget's disease of bone, cancer, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, polycythemia vera, essential thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express TREM2, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza.

TREM2-dependent gene expression

[0264] In some embodiments, anti-TREM2 antibodies of the present disclosure may increase the activity and/or expression of TREM2-dependent genes, such as one or more transcription factors of the nuclear factor of activated T-cells (NFAT) family of transcription factors.

[0265] In some embodiments, anti-TREM2 antibodies of the present disclosure may be beneficial for preventing, lowering the risk of, or treating conditions and/or diseases associated with

decreased levels of TREM2-dependent genes, including dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, tauopathy disease, Nasu-Hakola disease, stroke, acute trauma, chronic trauma, cognitive deficit, memory loss, lupus, acute and chronic colitis, rheumatoid arthritis, wound healing, Crohn's disease, inflammatory bowel disease, ulcerative colitis, obesity, malaria, essential tremor, central nervous system lupus, Behcet's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, Shy-Drager syndrome, progressive supranuclear palsy, cortical basal ganglionic degeneration, acute disseminated encephalomyelitis, granulomartous disorders, sarcoidosis, diseases of aging, seizures, spinal cord injury, traumatic brain injury, age related macular degeneration, glaucoma, retinitis pigmentosa, retinal degeneration, respiratory tract infection, sepsis, eye infection, systemic infection, lupus, arthritis, multiple sclerosis, low bone density, osteoporosis, osteogenesis, osteopetrotic disease, Paget's disease of bone, cancer, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, polycythemia vera, essential thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express TREM2, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza, comprising administering to an individual in need thereof a therapeutically effective amount of an agent that does not inhibit interaction between TREM2 and one or more TREM2 ligands, and/or enhance one or more activities of at least one TREM2 ligand. Other aspects of the present disclosure relate to an agent that does not inhibit interaction between TREM2 and one or more CD33 ligands for use in preventing, reducing risk, or treating a disease, disorder, or injury selected from dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, tauopathy disease, Nasu-Hakola disease, stroke, acute trauma, chronic trauma, cognitive deficit, memory loss, lupus, acute and chronic colitis, rheumatoid arthritis, wound healing, Crohn's disease, inflammatory bowel disease, ulcerative colitis, obesity, malaria, essential tremor, central nervous system lupus, Behcet's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, Shy-Drager syndrome, progressive supranuclear palsy, cortical basal ganglionic degeneration, acute disseminated encephalomyelitis, granulomartous disorders, sarcoidosis, diseases of aging, seizures, spinal cord injury, traumatic brain injury, age related macular degeneration, glaucoma, retinitis pigmentosa, retinal degeneration, respiratory tract infection, sepsis, eye infection, systemic infection, lupus, arthritis, multiple sclerosis, low bone density, osteoporosis,

osteogenesis, osteopetrotic disease, Paget's disease of bone, cancer, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin`s lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, polycythemia vera, essential thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express TREM2, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza.

Antibody preparation

[0266] Anti-TREM2 antibodies of the present disclosure can encompass polyclonal antibodies, monoclonal antibodies, humanized and chimeric antibodies, human antibodies, antibody fragments (*e.g.*, Fab, Fab'-SH, Fv, scFv, and $F(ab')_2$), bispecific and polyspecific antibodies, multivalent antibodies, library derived antibodies, antibodies having modified effector functions, fusion proteins containing an antibody portion, and any other modified configuration of the immunoglobulin molecule that includes an antigen recognition site, such as an epitope having amino acid residues of a TREM2 protein of the present disclosure, including glycosylation variants of antibodies, amino acid sequence variants of antibodies, and covalently modified antibodies. The anti-TREM2 antibodies may be human, murine, rat, or of any other origin (including chimeric or humanized antibodies).

(1) Polyclonal antibodies

[0267] Polyclonal antibodies, such as anti-TREM2 polyclonal antibodies, are generally raised in animals by multiple subcutaneous (sc) or intraperitoneal (ip) injections of the relevant antigen and an adjuvant. It may be useful to conjugate the relevant antigen (*e.g.*, a purified or recombinant TREM2 protein of the present disclosure) to a protein that is immunogenic in the species to be immunized, *e.g.*, keyhole limpet hemocyanin (KLH), serum albumin, bovine thyroglobulin, or soybean trypsin inhibitor, using a bifunctional or derivatizing agent, *e.g.*, maleimidobenzoyl sulfosuccinimide ester (conjugation through cysteine residues), N-hydroxysuccinimide (through lysine residues), glutaraldehyde, succinic anhydride, $SOCl_2$, or $R^1N{=}C{=}NR$, where R and R^1 are independently lower alkyl groups. Examples of adjuvants which may be employed include Freund's complete adjuvant and MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate). The immunization protocol may be selected by one skilled in the art without undue experimentation.

[0268] The animals are immunized against the desired antigen, immunogenic conjugates, or derivatives by combining, *e.g.*, 100 µg (for rabbits) or 5 µg (for mice) of the protein or conjugate with 3 volumes of Freund's complete adjuvant and injecting the solution intradermally at multiple sites.

One month later, the animals are boosted with 1/5 to 1/10 the original amount of peptide or conjugate in Freund's complete adjuvant by subcutaneous injection at multiple sites. Seven to fourteen days later, the animals are bled and the serum is assayed for antibody titer. Animals are boosted until the titer plateaus. Conjugates also can be made in recombinant-cell culture as protein fusions. Also, aggregating agents such as alum are suitable to enhance the immune response.

(2) Monoclonal antibodies

[0269] Monoclonal antibodies, such as anti-TREM2 monoclonal antibodies, are obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations and/or post-translational modifications (*e.g.*, isomerizations, amidations) that may be present in minor amounts. Thus, the modifier "monoclonal" indicates the character of the antibody as not being a mixture of discrete antibodies.

[0270] For example, the anti-TREM2 monoclonal antibodies may be made using the hybridoma method first described by Köhler et al., *Nature,* 256:495 (1975), or may be made by recombinant DNA methods (U.S. Patent No. 4,816,567).

[0271] In the hybridoma method, a mouse or other appropriate host animal, such as a hamster, is immunized as hereinabove described to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization (*e.g.*, a purified or recombinant TREM2 protein of the present disclosure). Alternatively, lymphocytes may be immunized *in vitro*. Lymphocytes then are fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, *Monoclonal Antibodies: Principles and Practice*, pp.59-103 (Academic Press, 1986)).

[0272] The immunizing agent will typically include the antigenic protein (*e.g.*, a purified or recombinant TREM2 protein of the present disclosure) or a fusion variant thereof. Generally peripheral blood lymphocytes ("PBLs") are used if cells of human origin are desired, while spleen or lymph node cells are used if non-human mammalian sources are desired. The lymphoctyes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell. Goding, *Monoclonal Antibodies: Principles and Practice*, Academic Press (1986), pp. 59-103.

[0273] Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine or human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells thus prepared are seeded and grown in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which are substances that prevent the growth of HGPRT-deficient-cells.

[0274] Preferred immortalized myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. Among these, preferred are murine myeloma lines, such as those derived from MOPC-21 and MPC-11 mouse tumors (available from the Salk Institute Cell Distribution Center, San Diego, California USA), as well as SP-2 cells and derivatives thereof (*e.g.*, X63-Ag8-653) (available from the American Type Culture Collection, Manassas, Virginia USA). Human myeloma and mouse-human heteromyeloma cell lines have also been described for the production of human monoclonal antibodies (Kozbor, *J. Immunol.*, 133:3001 (1984); Brodeur et al., *Monoclonal Antibody Production Techniques and Applications*, pp. 51-63 (Marcel Dekker, Inc., New York, 1987)).

[0275] Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against the antigen (*e.g.*, a TREM2 protein of the present disclosure). Preferably, the binding specificity of monoclonal antibodies produced by hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunosorbent assay (ELISA).

[0276] The culture medium in which the hybridoma cells are cultured can be assayed for the presence of monoclonal antibodies directed against the desired antigen (*e.g.*, a TREM2 protein of the present disclosure). Preferably, the binding affinity and specificity of the monoclonal antibody can be determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked assay (ELISA). Such techniques and assays are known in the in art. For example, binding affinity may be determined by the Scatchard analysis of Munson et al., *Anal. Biochem.*, 107:220 (1980).

[0277] After hybridoma cells are identified that produce antibodies of the desired specificity, affinity, and/or activity, the clones may be subcloned by limiting dilution procedures and grown by standard methods (Goding, *supra*). Suitable culture media for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells may be grown *in vivo* as tumors in a mammal.

[0278] The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose chromatography, hydroxylapatite chromatography, gel electrophoresis, dialysis, affinity chromatography, and other methods as described above.

[0279] Anti-TREM2 monoclonal antibodies may also be made by recombinant DNA methods, such as those disclosed in U.S. Patent No. 4,816,567, and as described above. DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that specifically bind to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host-cells such as *E. coli* cells, simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise

produce immunoglobulin protein, in order to synthesize monoclonal antibodies in such recombinant host-cells. Review articles on recombinant expression in bacteria of DNA encoding the antibody include Skerra et al., *Curr. Opin. Immunol.*, 5:256-262 (1993) and Plückthun, *Immunol. Rev.* 130:151-188 (1992).

[0280] In certain embodiments, anti-TREM2 antibodies can be isolated from antibody phage libraries generated using the techniques described in McCafferty et al., *Nature*, 348:552-554 (1990). Clackson et al., *Nature*, 352:624-628 (1991) and Marks et al., *J. Mol. Biol.*, 222:581-597 (1991) described the isolation of murine and human antibodies, respectively, from phage libraries. Subsequent publications describe the production of high affinity (nanomolar ("nM") range) human antibodies by chain shuffling (Marks et al., *Bio/Technology*, 10:779-783 (1992)), as well as combinatorial infection and *in vivo* recombination as a strategy for constructing very large phage libraries (Waterhouse et al., *Nucl. Acids Res.*, 21:2265-2266 (1993)). Thus, these techniques are viable alternatives to traditional monoclonal antibody hybridoma techniques for isolation of monoclonal antibodies of desired specificity (*e.g.*, those that bind a TREM2 protein of the present disclosure).

[0281] The DNA encoding antibodies or fragments thereof may also be modified, for example, by substituting the coding sequence for human heavy- and light-chain constant domains in place of the homologous murine sequences (U.S. Patent No. 4,816,567; Morrison, et al., *Proc. Natl Acad. Sci. USA*, 81:6851 (1984)), or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Typically such non-immunoglobulin polypeptides are substituted for the constant domains of an antibody, or they are substituted for the variable domains of one antigen-combining site of an antibody to create a chimeric bivalent antibody comprising one antigen-combining site having specificity for an antigen and another antigen-combining site having specificity for a different antigen.

[0282] The monoclonal antibodies described herein (*e.g.*, anti-TREM2 antibodies of the present disclosure or fragments thereof) may by monovalent, the preparation of which is well known in the art. For example, one method involves recombinant expression of immunoglobulin light chain and a modified heavy chain. The heavy chain is truncated generally at any point in the Fc region so as to prevent heavy chain crosslinking. Alternatively, the relevant cysteine residues may be substituted with another amino acid residue or are deleted so as to prevent crosslinking. *In vitro* methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly Fab fragments, can be accomplished using routine techniques known in the art.

[0283] Chimeric or hybrid anti-TREM2 antibodies also may be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide-exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate.

(3) Humanized antibodies

[0284] Anti-TREM2 antibodies of the present disclosure or antibody fragments thereof may further include humanized or human antibodies. Humanized forms of non-human (*e.g.*, murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fab, Fab'-SH, Fv, scFv, $F(ab')_2$ or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementarity determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally will also comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. Jones et al., *Nature* 321: 522-525 (1986); Riechmann et al., *Nature* 332: 323-329 (1988) and Presta, *Curr. Opin. Struct. Biol.* 2: 593-596 (1992).

[0285] Methods for humanizing non-human anti-TREM2 antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers, Jones et al., *Nature* 321:522-525 (1986); Riechmann et al., *Nature* 332:323-327 (1988); Verhoeyen et al., *Science* 239:1534-1536 (1988), or through substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

[0286] The choice of human variable domains, both light and heavy, to be used in making the humanized antibodies is very important to reduce antigenicity. According to the so-called "best-fit" method, the sequence of the variable domain of a rodent antibody is screened against the entire library of known human variable-domain sequences. The human sequence which is closest to that of the rodent is then accepted as the human framework (FR) for the humanized antibody. Sims et al., *J. Immunol.*, 151:2296 (1993); Chothia et al., *J. Mol. Biol.*, 196:901 (1987). Another method uses a particular framework derived from the consensus sequence of all human antibodies of a particular

subgroup of light or heavy chains. The same framework may be used for several different humanized antibodies. Carter et al., *Proc. Nat'l Acad. Sci. USA* 89:4285 (1992); Presta et al., *J. Immunol.* 151:2623 (1993).

[0287] Furthermore, it is important that antibodies be humanized with retention of high affinity for the antigen and other favorable biological properties. To achieve this goal, according to a preferred method, humanized antibodies are prepared by a process of analyzing the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, *i.e.*, the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, FR residues can be selected and combined from the recipient and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen or antigens (*e.g.*, TREM2 proteins of the present disclosure), is achieved. In general, the CDR residues are directly and most substantially involved in influencing antigen binding.

[0288] Various forms of the humanized anti-TREM2 antibody are contemplated. For example, the humanized anti-TREM2 antibody may be an antibody fragment, such as an Fab, which is optionally conjugated with one or more TREM2 ligand, such as HSP60. Alternatively, the humanized anti-TREM2 antibody may be an intact antibody, such as an intact IgG1 antibody.

(4) Antibody fragments

[0289] In certain embodiments there are advantages to using anti-TREM2 antibody fragments, rather than whole anti-TREM2 antibodies. In some embodiments, smaller fragment sizes allow for rapid clearance and better brain penetration.

[0290] Various techniques have been developed for the production of antibody fragments. Traditionally, these fragments were derived via proteolytic digestion of intact antibodies (*see, e.g.*, Morimoto et al., *J. Biochem. Biophys. Method.* 24:107-117 (1992); and Brennan et al., *Science* 229:81 (1985)). However, these fragments can now be produced directly by recombinant host-cells, for example, using nucleic acids encoding anti-TREM2 antibodies of the present disclosure. Fab, Fv and scFv antibody fragments can all be expressed in and secreted from *E. coli*, thus allowing the straightforward production of large amounts of these fragments. Anti-TREM2 antibody fragments can also be isolated from the antibody phage libraries as discussed above. Alternatively, Fab'-SH fragments can be directly recovered from *E. coli* and chemically coupled to form $F(ab')_2$ fragments (Carter et al., *Bio/Technology* 10:163-167 (1992)). According to another approach, $F(ab')_2$ fragments can be isolated directly from recombinant host-cell culture. Production of Fab and $F(ab')_2$ antibody fragments with increased *in vivo* half-lives are described in U.S. Patent No. 5,869,046. In other

embodiments, the antibody of choice is a single chain Fv fragment (scFv). See WO 93/16185; U.S. Patent No. 5,571,894 and U.S. Patent No. 5,587,458. The anti-TREM2 antibody fragment may also be a "linear antibody," *e.g.*, as described in U.S. Patent 5,641,870. Such linear antibody fragments may be monospecific or bispecific.

(5) Bispecific and polyspecific antibodies

[0291] Bispecific antibodies (BsAbs) are antibodies that have binding specificities for at least two different epitopes, including those on the same or another protein (*e.g.*, one or more TREM2 proteins of the present disclosure). Alternatively, one part of a BsAb can be armed to bind to the target TREM2 antigen, and another can be combined with an arm that binds to a second protein. Such antibodies can be derived from full-length antibodies or antibody fragments (*e.g.*, $F(ab')_2$ bispecific antibodies).

[0292] Methods for making bispecific antibodies are known in the art. Traditional production of full-length bispecific antibodies is based on the coexpression of two immunoglobulin heavy-chain/light chain pairs, where the two chains have different specificities. Millstein et al., *Nature*, 305:537-539 (1983). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of 10 different antibody molecules, of which only one has the correct bispecific structure. Purification of the correct molecule, which is usually done by affinity chromatography steps, is rather cumbersome, and the product yields are low. Similar procedures are disclosed in WO 93/08829 and in Traunecker et al., *EMBO J.*, 10:3655-3659 (1991).

[0293] According to a different approach, antibody variable domains with the desired binding specificities (antibody-antigen combining sites) are fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy chain constant domain, comprising at least part of the hinge, C_H2, and C_H3 regions. It is preferred to have the first heavy-chain constant region (C_H1) containing the site necessary for light chain binding, present in at least one of the fusions. DNAs encoding the immunoglobulin heavy chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. This provides for great flexibility in adjusting the mutual proportions of the three polypeptide fragments in embodiments when unequal ratios of the three polypeptide chains used in the construction provide the optimum yields. It is, however, possible to insert the coding sequences for two or all three polypeptide chains in one expression vector when the expression of at least two polypeptide chains in equal ratios results in high yields or when the ratios are of no particular significance.

[0294] In a preferred embodiment of this approach, the bispecific antibodies are composed of a hybrid immunoglobulin heavy chain with a first binding specificity in one arm, and a hybrid immunoglobulin heavy chain-light chain pair (providing a second binding specificity) in the other arm. It was found that this asymmetric structure facilitates the separation of the desired bispecific

compound from unwanted immunoglobulin chain combinations, as the presence of an immunoglobulin light chain in only half of the bispecific molecules provides for an easy way of separation. This approach is disclosed in WO 94/04690. For further details of generating bispecific antibodies, see, for example, Suresh et al., *Methods in Enzymology* 121: 210 (1986); and Garber, *Nature Reviews Drug Discovery* 13, 799-801 (2014).

[0295] According to another approach described in WO 96/27011 or U.S. Patent No. 5,731,168, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant-cell culture. The preferred interface comprises at least a part of the C_H3 region of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (*e.g.*, tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chains(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (*e.g.*, alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

[0296] Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan et al., *Science* 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate $F(ab')_2$ fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

[0297] Fab' fragments may be directly recovered from *E. coli* and chemically coupled to form bispecific antibodies. Shalaby et al., *J. Exp. Med.* 175: 217-225 (1992) describes the production of fully humanized bispecific antibody $F(ab')_2$ molecules. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling *in vitro* to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T-cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

[0298] Various techniques for making and isolating bivalent antibody fragments directly from recombinant-cell culture have also been described. For example, bivalent heterodimers have been produced using leucine zippers. Kostelny et al., *J. Immunol.*, 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. The "diabody" technology described by Hollinger et al., *Proc. Nat'l Acad. Sci. USA*, 90: 6444-6448 (1993) has provided an

alternative mechanism for making bispecific/bivalent antibody fragments. The fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific/bivalent antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. *See* Gruber et al., *J. Immunol.*, 152:5368 (1994).

[0299] Another method to generate bispecific antibodies is designated controlled Fab-arm exchange (cFAE), which is an easy-to-use method to generate bispecific IgG1 (bsIgG1). The protocol involves the following: (i) separate expression of two parental IgG1s containing single matching point mutations in the CH3 domain; (ii) mixing of parental IgG1s under permissive redox conditions in vitro to enable recombination of half-molecules; (iii) removal of the reductant to allow reoxidation of interchain disulfide bonds; and (iv) analysis of exchange efficiency and final product using chromatography-based or mass spectrometry (MS)–based methods. The protocol generates bsAbs with regular IgG architecture, characteristics and quality attributes both at bench scale (micrograms to milligrams) and at a mini-bioreactor scale (milligrams to grams) that is designed to model large-scale manufacturing (kilograms). Starting from good-quality purified proteins, exchange efficiencies of ≥95% can be obtained within 2-3 days (including quality control). *See* Labrijn et al., *Natur Protocols* 9, 2450-2463 (2014); and Garber, *Nature Reviews Drug Discovery* 13, 799-801 (2014).

[0300] Antibodies with more than two valencies are also contemplated. For example, trispecific antibodies can be prepared. Tutt et al., *J. Immunol.* 147:60 (1991).

[0301] Exemplary bispecific antibodies may bind to two different epitopes on a given molecule (*e.g.*, a TREM2 protein of the present disclosure). In some embodiments a bispecific antibody binds to a first antigen, such as a TREM2 or DAP12 protein of the present disclosure, and a second antigen facilitating transport across the blood-brain barrier. Numerous antigens are known in the art that facilitate transport across the blood-brain barrier (*see*, *e.g.*, Gabathuler R., Approaches to transport therapeutic drugs across the blood-brain barrier to treat brain diseases, Neurobiol. Dis. 37 (2010) 48-57). Such second antigens include, without limitation, 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, including CRM197 (a non-toxic mutant of diphtheria toxin), llama single domain antibodies such as TMEM 30(A) (Flippase), protein transduction domains such as TAT, Syn-B, or penetratin, poly-arginine or generally positively charged peptides, Angiopep peptides such as ANG1005 (*see*, *e.g.*, Gabathuler, 2010), and other cell surface proteins that are enriched on blood-brain barrier endothelial cells (*see*, *e.g.*, Daneman et al., PLoS One. 2010 Oct 29;5(10):e13741). In some embodiments, second antigens for an anti-TREM2 antibody may include, without limitation, a DAP12 antigen of the present disclosure. In other embodiments, bispecific antibodies that bind to both TREM2 and DAP12 may facilitate and enhance one or more TREM2

activities. In other embodiments, second antigens for an anti-TREM2 antibody may include, without limitation, A beta peptide, antigen or an alpha synuclein protein antigen or, Tau protein antigen or, TDP-43 protein antigen or, prion protein antigen or, huntingtin protein antigen, or RAN, translation Products antigen, including the DiPeptide Repeats,(DPRs peptides) composed of glycine-alanine (GA), glycine-proline (GP), glycine-arginine (GR), proline-alanine (PA), or proline-arginine (PR).

(6) Multivalent antibodies

[0302] A multivalent antibody may be internalized (and/or catabolized) faster than a bivalent antibody by a cell expressing an antigen to which the antibodies bind. The anti-TREM2 antibodies of the present disclosure or antibody fragments thereof can be multivalent antibodies (which are other than of the IgM class) with three or more antigen binding sites (*e.g.*, tetravalent antibodies), which can be readily produced by recombinant expression of nucleic acid encoding the polypeptide chains of the antibody. The multivalent antibody can comprise a dimerization domain and three or more antigen binding sites. The preferred dimerization domain comprises an Fc region or a hinge region. In this scenario, the antibody will comprise an Fc region and three or more antigen binding sites amino-terminal to the Fc region. The preferred multivalent antibody herein contains three to about eight, but preferably four, antigen binding sites. The multivalent antibody contains at least one polypeptide chain (and preferably two polypeptide chains), wherein the polypeptide chain or chains comprise two or more variable domains. For instance, the polypeptide chain or chains may comprise VD1-(X1)n-VD2-(X2)n-Fc, wherein VD1 is a first variable domain, VD2 is a second variable domain, Fc is one polypeptide chain of an Fc region, X1 and X2 represent an amino acid or polypeptide, and n is 0 or 1. Similarly, the polypeptide chain or chains may comprise V_H-C_H1-flexible linker-V_H-C_H1-Fc region chain; or V_H-C_H1-V_H-C_H1-Fc region chain. The multivalent antibody herein preferably further comprises at least two (and preferably four) light chain variable domain polypeptides. The multivalent antibody herein may, for instance, comprise from about two to about eight light chain variable domain polypeptides. The light chain variable domain polypeptides contemplated here comprise a light chain variable domain and, optionally, further comprise a CL domain. The Multivalent antibodies may recognize the TREM2 antigen as well as without limitation additional antigens A beta peptide, antigen or an alpha synuclein protein antigen or, Tau protein antigen or, TDP-43 protein antigen or, prion protein antigen or, huntingtin protein antigen, or RAN, translation Products antigen, including the DiPeptide Repeats,(DPRs peptides) composed of glycine-alanine (GA), glycine-proline (GP), glycine-arginine (GR), proline-alanine (PA), or proline-arginine (PR), Insulin receptor, insulin like growth factor receptor. Transferrin receptor or any other antigen that facilitate antibody transfer across the blood brain barrier.

(7) Effector function engineering

It may also be desirable to modify an anti-TREM2 antibody of the present disclosure to modify effector function and/or to increase serum half-life of the antibody. For example, the Fc receptor binding site on the constant region may be modified or mutated to remove or reduce binding affinity

to certain Fc receptors, such as FcγRI, FcγRII, and/or FcγRIII to reduce Antibody-dependent cell-mediated cytotoxicity. In some embodiments, the effector function is impaired by removing N-glycosylation of the Fc region (*e.g.*, in the CH 2 domain of IgG) of the antibody. In some embodiments, the effector function is impaired by modifying regions such as 233-236, 297, and/or 327-331 of human IgG as described in PCT WO 99/58572 and Armour et al., *Molecular Immunology* 40: 585-593 (2003); Reddy et al., *J. Immunology* 164:1925-1933 (2000). In other embodiments, it may also be desirable to modify an anti-TREM2 antibody of the present disclosure to modify effector function to increase finding selectivity toward the ITIM-containing FcgRIIb (CD32b) to increase clustering of TREM2 antibodies on adjacent cells without activating humoral responses including Antibody-dependent cell-mediated cytotoxicity and antibody-dependent cellular phagocytosis.

[0303] To increase the serum half-life of the antibody, one may incorporate a salvage receptor binding epitope into the antibody (especially an antibody fragment) as described in U.S. Patent 5,739,277, for example. As used herein, the term "*salvage receptor binding epitope*" refers to an epitope of the Fc region of an IgG molecule (*e.g.*, IgG_1, IgG_2, IgG_3, or IgG_4) that is responsible for increasing the *in vivo* serum half-life of the IgG molecule.

(8) Other amino acid sequence modifications

[0304] Amino acid sequence modifications of anti-TREM2 antibodies of the present disclosure, or antibody fragments thereof, are also contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the antibodies or antibody fragments. Amino acid sequence variants of the antibodies or antibody fragments are prepared by introducing appropriate nucleotide changes into the nucleic acid encoding the antibodies or antibody fragments, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of, residues within the amino acid sequences of the antibody. Any combination of deletion, insertion, and substitution is made to arrive at the final construct, provided that the final construct possesses the desired characteristics (*i.e.*, the ability to bind or physically interact with a TREM2 protein of the present disclosure). The amino acid changes also may alter post-translational processes of the antibody, such as changing the number or position of glycosylation sites.

[0305] A useful method for identification of certain residues or regions of the anti-TREM2 antibody that are preferred locations for mutagenesis is called "alanine scanning mutagenesis" as described by Cunningham and Wells in *Science*, 244:1081-1085 (1989). Here, a residue or group of target residues are identified (*e.g.*, charged residues such as arg, asp, his, lys, and glu) and replaced by a neutral or negatively charged amino acid (most preferably alanine or polyalanine) to affect the interaction of the amino acids with the target antigen. Those amino acid locations demonstrating functional sensitivity to the substitutions then are refined by introducing further or other variants at, or for, the sites of substitution. Thus, while the site for introducing an amino acid sequence variation is predetermined, the nature of the mutation *per se* need not be predetermined. For example, to analyze

the performance of a mutation at a given site, alanine scanning or random mutagenesis is conducted at the target codon or region and the expressed antibody variants are screened for the desired activity.

[0306] Amino acid sequence insertions include amino- ("N") and/or carboxy- ("C") terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an antibody with an N-terminal methionyl residue or the antibody fused to a cytotoxic polypeptide. Other insertional variants of the antibody molecule include the fusion to the N- or C-terminus of the antibody to an enzyme or a polypeptide which increases the serum half-life of the antibody.

[0307] Another type of variant is an amino acid substitution variant. These variants have at least one amino acid residue in the antibody molecule replaced by a different residue. The sites of greatest interest for substitutional mutagenesis include the hypervariable regions, but FR alterations are also contemplated. Conservative substitutions are shown in the Table C below under the heading of "preferred substitutions". If such substitutions result in a change in biological activity, then more substantial changes, denominated "exemplary substitutions" in Table B, or as further described below in reference to amino acid classes, may be introduced and the products screened.

TABLE B: Amino Acid Substitutions

Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	val; leu; ile	val
Arg (R)	lys; gln; asn	lys
Asn (N)	gln; his; asp, lys; arg	gln
Asp (D)	glu; asn	glu
Cys (C)	ser; ala	ser
Gln (Q)	asn; glu	asn
Glu (E)	asp; gln	asp
Gly (G)	ala	ala
His (H)	asn; gln; lys; arg	arg
Ile (I)	leu; val; met; ala; phe; norleucine	leu
Leu (L)	norleucine; ile; val; met; ala; phe	ile
Lys (K)	arg; gln; asn	arg
Met (M)	leu; phe; ile	leu
Phe (F)	leu; val; ile; ala; tyr	tyr
Pro (P)	ala	ala
Ser (S)	thr	thr
Thr (T)	ser	ser
Trp (W)	tyr; phe	tyr
Tyr (Y)	trp; phe; thr; ser	phe
Val (V)	ile; leu; met; phe; ala; norleucine	leu

[0308] Substantial modifications in the biological properties of the antibody are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation,

(b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

(1) hydrophobic: norleucine, met, ala, val, leu, ile;

(2) neutral hydrophilic: cys, ser, thr;

(3) acidic: asp, glu;

(4) basic: asn, gln, his, lys, arg;

(5) residues that influence chain orientation: gly, pro; and

(6) aromatic: trp, tyr, phe.

[0309] Non-conservative substitutions entail exchanging a member of one of these classes for another class.

[0310] Any cysteine residue not involved in maintaining the proper conformation of the antibody also may be substituted, generally with serine, to improve the oxidative stability of the molecule and prevent aberrant crosslinking. Conversely, cysteine bond(s) may be added to the antibody to improve its stability (particularly where the antibody is an antibody fragment, such as an Fv fragment).

[0311] A particularly preferred type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody (*e.g.* a humanized or human anti-TREM2 antibody). Generally, the resulting variant(s) selected for further development will have improved biological properties relative to the parent antibody from which they are generated. A convenient way for generating such substitutional variants involves affinity maturation using phage display. Briefly, several hypervariable region sites (*e.g.*, 6-7 sites) are mutated to generate all possible amino substitutions at each site. The antibody variants thus generated are displayed in a monovalent fashion from filamentous phage particles as fusions to the gene III product of M13 packaged within each particle. The phage-displayed variants are then screened for their biological activity (*e.g.*, binding affinity) as herein disclosed. In order to identify candidate hypervariable region sites for modification, alanine scanning mutagenesis can be performed to identify hypervariable region residues contributing significantly to antigen binding. Alternatively, or additionally, it may be beneficial to analyze a crystal structure of the antigen-antibody complex to identify contact points between the antibody and the antigen (*e.g.*, a TREM2 protein of the present disclosure). Such contact residues and neighboring residues are candidates for substitution according to the techniques elaborated herein. Once such variants are generated, the panel of variants is subjected to screening as described herein and antibodies with superior properties in one or more relevant assays may be selected for further development. Affinity maturation may also be performed by employing a yeast presentation technology such as that disclosed in, for example, WO2009/036379A2; WO2010105256; WO2012009568; and Xu et al., *Protein Eng. Des. Sel.*, 26(10): 663-70 (2013).

[0312] Another type of amino acid variant of the antibody alters the original glycosylation pattern of the antibody. By altering is meant deleting one or more carbohydrate moieties found in the antibody, and/or adding one or more glycosylation sites that are not present in the antibody.

[0313] Glycosylation of antibodies is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tripeptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tripeptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-aceylgalactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used.

[0314] Addition of glycosylation sites to the antibody is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tripeptide sequences (for N-linked glycosylation sites). The alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues to the sequence of the original antibody (for O-linked glycosylation sites).

[0315] Nucleic acid molecules encoding amino acid sequence variants of the anti-IgE antibody are prepared by a variety of methods known in the art. These methods include, but are not limited to, isolation from a natural source (in the case of naturally occurring amino acid sequence variants) or preparation by oligonucleotide-mediated (or site-directed) mutagenesis, PCR mutagenesis, and cassette mutagenesis of an earlier prepared variant or a non-variant version of the antibodies (*e.g.*, anti-TREM2 antibodies of the present disclosure) or antibody fragments.

(9) Other antibody modifications

[0316] Anti-TREM2 antibodies of the present disclosure, or antibody fragments thereof, can be further modified to contain additional non-proteinaceous moieties that are known in the art and readily available, or to contain different types of drug conjugates that are known in the art and readily available. Preferably, the moieties suitable for derivatization of the antibody are water-soluble polymers. Non-limiting examples of water-soluble polymers include, but are not limited to, polyethylene glycol (PEG), copolymers of ethylene glycol/propylene glycol, carboxymethylcellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone, poly-1, 3-dioxolane, poly-1,3,6-trioxane, ethylene/maleic anhydride copolymer, polyaminoacids (either homopolymers or random copolymers), and dextran or poly(n-vinyl pyrrolidone)polyethylene glycol, polypropylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols (*e.g.*, glycerol), polyvinyl alcohol, and mixtures thereof. Polyethylene glycol propionaldehyde may have advantages in manufacturing due to its stability in water. The polymer may be of any molecular weight, and may be branched or unbranched. The number of polymers attached to the antibody may vary, and if more than one polymer is attached, they can be the same or different molecules. In general, the number and/or type of polymers used for derivatization can be determined based on considerations including, but not limited to, the particular properties or functions of the antibody to be improved, whether the antibody derivative will be used in a therapy under defined conditions, *etc.* Such techniques and other suitable

formulations are disclosed in *Remington: The Science and Practice of Pharmacy*, 20th Ed., Alfonso Gennaro, Ed., Philadelphia College of Pharmacy and Science (2000).

[0317] Drug conjugation involves coupling of a biological active cytotoxic (anticancer) payload or drug to an antibody that specifically targets a certain tumor marker (*e.g.* a protein that, ideally, is only to be found in or on tumor cells). Antibodies track these proteins down in the body and attach themselves to the surface of cancer cells. The biochemical reaction between the antibody and the target protein (antigen) triggers a signal in the tumor cell, which then absorbs or internalizes the antibody together with the cytotoxin. After the ADC is internalized, the cytotoxic drug is released and kills the cancer. Due to this targeting, ideally the drug has lower side effects and gives a wider therapeutic window than other chemotherapeutic agents. Technics to conjugate antibodies are disclosed are known in the art (*see, e.g.*, Jane de Lartigue, OncLive July 5, 2012; ADC Review on antibody-drug conjugates; and Ducry et al., (2010). *Bioconjugate Chemistry* 21 (1): 5–13).

Binding assays and other assays

[0318] Anti-TREM2 antibodies of the present disclosure may be tested for antigen binding activity, *e.g.*, by known methods such as ELISA, Western blot, *etc.*

[0319] In some embodiments, competition assays may be used to identify an antibody that competes with any of the antibodies listed in **Tables 2A-2C, 3A-3C, 4A-4D, 5A-5D, 6, and 7**, or selected from 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 for binding to TREM2. In certain embodiments, such a competing antibody binds to the same epitope (*e.g.*, a linear or a conformational epitope) that is bound by any of the antibodies listed in **Tables 2A-2C, 3A-3C, 4A-4D, 5A-5D, 6, and 7**, or selected from 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. Detailed exemplary methods for mapping an epitope to which an antibody binds are provided in Morris (1996) "Epitope Mapping Protocols," in *Methods in Molecular Biology* vol. 66 (Humana Press, Totowa, NJ).

[0320] In an exemplary competition assay, immobilized TREM2 or cells expressing TREM2 on cell surface are incubated in a solution comprising a first labeled antibody that binds to TREM2 (*e.g.*, human or non-human primate) and a second unlabeled antibody that is being tested for its ability to compete with the first antibody for binding to TREM2. The second antibody may be present in a hybridoma supernatant. As a control, immobilized TREM2 or cells expressing TREM2 is incubated in a solution comprising the first labeled antibody but not the second unlabeled antibody. After incubation under conditions permissive for binding of the first antibody to TREM2, excess unbound antibody is removed, and the amount of label associated with immobilized TREM2 or cells expressing TREM2 is measured. If the amount of label associated with immobilized TREM2 or cells expressing TREM2 is substantially reduced in the test sample relative to the control sample, then that indicates that the second antibody is competing with the first antibody for binding to TREM2. See Harlow and Lane (1988) *Antibodies: A Laboratory Manual* ch.14 (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY).

Nucleic acids, vectors, and host cells

[0321] Anti-TREM2 antibodies of the present disclosure may be produced using recombinant methods and compositions, *e.g.*, as described in U.S. Patent No. 4,816,567. In some embodiments, isolated nucleic acids having a nucleotide sequence encoding any of the anti-TREM2 antibodies of the present disclosure are provided. Such nucleic acids may encode an amino acid sequence containing the VL and/or an amino acid sequence containing the VH of the anti-TREM2 antibody (*e.g.*, the light and/or heavy chains of the antibody). In some embodiments, one or more vectors (*e.g.*, expression vectors) containing such nucleic acids are provided. In some embodiments, a host cell containing such nucleic acid is also provided. In some embodiments, the host cell contains (*e.g.*, has been transduced with): (1) a vector containing a nucleic acid that encodes an amino acid sequence containing the VL of the antibody and an amino acid sequence containing the VH of the antibody, or (2) a first vector containing a nucleic acid that encodes an amino acid sequence containing the VL of the antibody and a second vector containing a nucleic acid that encodes an amino acid sequence containing the VH of the antibody. In some embodiments, the host cell is eukaryotic, *e.g.*, a Chinese Hamster Ovary (CHO) cell or lymphoid cell (*e.g.*, Y0, NS0, Sp20 cell). Host cells of the present disclosure also include, without limitation, isolated cells, *in vitro* cultured cells, and *ex vivo* cultured cells.

[0322] Methods of making an anti-TREM2 antibody of the present disclosure are provided. In some embodiments, the method includes culturing a host cell of the present disclosure containing a

nucleic acid encoding the anti-TREM2 antibody, under conditions suitable for expression of the antibody. In some embodiments, the antibody is subsequently recovered from the host cell (or host cell culture medium).

[0323] For recombinant production of an anti-TREM2 antibody of the present disclosure, a nucleic acid encoding the anti-TREM2 antibody is isolated and inserted into one or more vectors for further cloning and/or expression in a host cell. Such nucleic acid may be readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody).

[0324] Suitable vectors containing a nucleic acid sequence encoding any of the anti-TREM2 antibodies of the present disclosure, or fragments thereof polypeptides (including antibodies) described herein include, without limitation, cloning vectors and expression vectors. Suitable cloning vectors can be constructed according to standard techniques, or may be selected from a large number of cloning vectors available in the art. While the cloning vector selected may vary according to the host cell intended to be used, useful cloning vectors generally have the ability to self-replicate, may possess a single target for a particular restriction endonuclease, and/or may carry genes for a marker that can be used in selecting clones containing the vector. Suitable examples include plasmids and bacterial viruses, *e.g.*, pUC18, pUC19, Bluescript (*e.g.*, pBS SK+) and its derivatives, mpl8, mpl9, pBR322, pMB9, ColE1, pCR1, RP4, phage DNAs, and shuttle vectors such as pSA3 and pAT28. These and many other cloning vectors are available from commercial vendors such as BioRad, Strategene, and Invitrogen.

[0325] Expression vectors generally are replicable polynucleotide constructs that contain a nucleic acid of the present disclosure. The expression vector may replicable in the host cells either as episomes or as an integral part of the chromosomal DNA. Suitable expression vectors include but are not limited to plasmids, viral vectors, including adenoviruses, adeno-associated viruses, retroviruses, cosmids, and expression vector(s) disclosed in PCT Publication No. WO 87/04462. Vector components may generally include, but are not limited to, one or more of the following: a signal sequence; an origin of replication; one or more marker genes; suitable transcriptional controlling elements (such as promoters, enhancers and terminator). For expression (*i.e.*, translation), one or more translational controlling elements are also usually required, such as ribosome binding sites, translation initiation sites, and stop codons.

[0326] The vectors containing the nucleic acids of interest can be introduced into the host cell by any of a number of appropriate means, including electroporation, transfection employing calcium chloride, rubidium chloride, calcium phosphate, DEAE-dextran, or other substances; microprojectile bombardment; lipofection; and infection (*e.g.*, where the vector is an infectious agent such as vaccinia virus). The choice of introducing vectors or polynucleotides will often depend on features of the host cell. In some embodiments, the vector contains a nucleic acid containing one or more amino acid sequences encoding an anti-TREM2 antibody of the present disclosure.

[0327] Suitable host cells for cloning or expression of antibody-encoding vectors include prokaryotic or eukaryotic cells. For example, anti-TREM2 antibodies of the present disclosure may be produced in bacteria, in particular when glycosylation and Fc effector function are not needed. For expression of antibody fragments and polypeptides in bacteria (*e.g.*, U.S. Patent Nos. 5,648,237, 5,789,199, and 5,840,523; and Charlton, *Methods in Molecular Biology, Vol. 248* (B.K.C. Lo, ed., Humana Press, Totowa, NJ, 2003), pp. 245-254, describing expression of antibody fragments in *E. coli*.). After expression, the antibody may be isolated from the bacterial cell paste in a soluble fraction and can be further purified.

[0328] In addition to prokaryotes, eukaryotic microorganisms, such as filamentous fungi or yeast, are also suitable cloning or expression hosts for antibody-encoding vectors, including fungi and yeast strains whose glycosylation pathways have been "humanized," resulting in the production of an antibody with a partially or fully human glycosylation pattern (*e.g.*, Gerngross, *Nat. Biotech.* 22:1409-1414 (2004); and Li et al., *Nat. Biotech.* 24:210-215 (2006)).

[0329] Suitable host cells for the expression of glycosylated antibody can also be derived from multicellular organisms (invertebrates and vertebrates). Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains have been identified which may be used in conjunction with insect cells, particularly for transfection of *Spodoptera frugiperda* cells. Plant cell cultures can also be utilized as hosts (*e.g.*, U.S. Patent Nos. 5,959,177, 6,040,498, 6,420,548, 7,125,978, and 6,417,429, describing PLANTIBODIES™ technology for producing antibodies in transgenic plants.).

[0330] Vertebrate cells may also be used as hosts. For example, mammalian cell lines that are adapted to grow in suspension may be useful. Other examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7); human embryonic kidney line (293 or 293 cells as described, *e.g.*, in Graham et al., *J. Gen Virol.* 36:59 (1977)); baby hamster kidney cells (BHK); mouse sertoli cells (TM4 cells as described, *e.g.*, in Mather, *Biol. Reprod.* 23:243-251 (1980)); monkey kidney cells (CV1); African green monkey kidney cells (VERO-76); human cervical carcinoma cells (HELA); canine kidney cells (MDCK; buffalo rat liver cells (BRL 3A); human lung cells (W138); human liver cells (Hep G2); mouse mammary tumor (MMT 060562); TRI cells, as described, *e.g.*, in Mather et al., *Annals N.Y. Acad. Sci.* 383:44-68 (1982); MRC 5 cells; and FS4 cells. Other useful mammalian host cell lines include Chinese hamster ovary (CHO) cells, including DHFR-CHO cells (Urlaub et al., *Proc. Natl. Acad. Sci. USA* 77:4216 (1980)); and myeloma cell lines such as Y0, NS0 and Sp2/0. For a review of certain mammalian host cell lines suitable for antibody production, see, *e.g.*, Yazaki and Wu, *Methods in Molecular Biology, Vol. 248* (B.K.C. Lo, ed., Humana Press, Totowa, NJ), pp. 255-268 (2003).

Pharmaceutical compositions

[0331] Anti-TREM2 antibodies of the present disclosure can be incorporated into a variety of formulations for therapeutic administration by combining the antibodies with appropriate

pharmaceutically acceptable carriers or diluents, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms. Examples of such formulations include, without limitation, tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants, gels, microspheres, and aerosols. Pharmaceutical compositions can include, depending on the formulation desired, pharmaceutically-acceptable, non-toxic carriers of diluents, which are vehicles commonly used to formulate pharmaceutical compositions for animal or human administration. The diluent is selected so as not to affect the biological activity of the combination. Examples of such diluents include, without limitation, distilled water, buffered water, physiological saline, PBS, Ringer's solution, dextrose solution, and Hank's solution. A pharmaceutical composition or formulation of the present disclosure can further include other carriers, adjuvants, or non-toxic, nontherapeutic, nonimmunogenic stabilizers, excipients and the like. The compositions can also include additional substances to approximate physiological conditions, such as pH adjusting and buffering agents, toxicity adjusting agents, wetting agents and detergents.

[0332] A pharmaceutical composition of the present disclosure can also include any of a variety of stabilizing agents, such as an antioxidant for example. When the pharmaceutical composition includes a polypeptide, the polypeptide can be complexed with various well-known compounds that enhance the *in vivo* stability of the polypeptide, or otherwise enhance its pharmacological properties (*e.g.*, increase the half-life of the polypeptide, reduce its toxicity, and enhance solubility or uptake). Examples of such modifications or complexing agents include, without limitation, sulfate, gluconate, citrate and phosphate. The polypeptides of a composition can also be complexed with molecules that enhance their *in vivo* attributes. Such molecules include, without limitation, carbohydrates, polyamines, amino acids, other peptides, ions (*e.g.*, sodium, potassium, calcium, magnesium, manganese), and lipids.

[0333] Further examples of formulations that are suitable for various types of administration can be found in Remington's *Pharmaceutical Sciences*, Mace Publishing Company, Philadelphia, PA, 17th ed. (1985). For a brief review of methods for drug delivery, see, Langer, *Science* 249:1527-1533 (1990).

[0334] For oral administration, the active ingredient can be administered in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. The active component(s) can be encapsulated in gelatin capsules together with inactive ingredients and powdered carriers, such as glucose, lactose, sucrose, mannitol, starch, cellulose or cellulose derivatives, magnesium stearate, stearic acid, sodium saccharin, talcum, magnesium carbonate. Examples of additional inactive ingredients that may be added to provide desirable color, taste, stability, buffering capacity, dispersion or other known desirable features are red iron oxide, silica gel, sodium lauryl sulfate, titanium dioxide, and edible white ink. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets

can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric-coated for selective disintegration in the gastrointestinal tract. Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

[0335] Formulations suitable for parenteral administration include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives.

[0336] The components used to formulate the pharmaceutical compositions are preferably of high purity and are substantially free of potentially harmful contaminants (*e.g.*, at least National Food (NF) grade, generally at least analytical grade, and more typically at least pharmaceutical grade). Moreover, compositions intended for *in vivo* use are usually sterile. To the extent that a given compound must be synthesized prior to use, the resulting product is typically substantially free of any potentially toxic agents, particularly any endotoxins, which may be present during the synthesis or purification process. Compositions for parental administration are also sterile, substantially isotonic and made under GMP conditions.

[0337] Formulations may be optimized for retention and stabilization in the brain or central nervous system. When the agent is administered into the cranial compartment, it is desirable for the agent to be retained in the compartment, and not to diffuse or otherwise cross the blood brain barrier. Stabilization techniques include cross-linking, multimerizing, or linking to groups such as polyethylene glycol, polyacrylamide, neutral protein carriers, *etc.* in order to achieve an increase in molecular weight.

[0338] Other strategies for increasing retention include the entrapment of the antibody, such as an anti-TREM2 antibody of the present disclosure, in a biodegradable or bioerodible implant. The rate of release of the therapeutically active agent is controlled by the rate of transport through the polymeric matrix, and the biodegradation of the implant. The transport of drug through the polymer barrier will also be affected by compound solubility, polymer hydrophilicity, extent of polymer cross-linking, expansion of the polymer upon water absorption so as to make the polymer barrier more permeable to the drug, geometry of the implant, and the like. The implants are of dimensions commensurate with the size and shape of the region selected as the site of implantation. Implants may be particles, sheets, patches, plaques, fibers, microcapsules and the like and may be of any size or shape compatible with the selected site of insertion.

[0339] The implants may be monolithic, *i.e.* having the active agent homogenously distributed through the polymeric matrix, or encapsulated, where a reservoir of active agent is encapsulated by the polymeric matrix. The selection of the polymeric composition to be employed will vary with the site of administration, the desired period of treatment, patient tolerance, the nature of the disease to be treated and the like. Characteristics of the polymers will include biodegradability at the site of

implantation, compatibility with the agent of interest, ease of encapsulation, a half-life in the physiological environment.

[0340] Biodegradable polymeric compositions which may be employed may be organic esters or ethers, which when degraded result in physiologically acceptable degradation products, including the monomers. Anhydrides, amides, orthoesters or the like, by themselves or in combination with other monomers, may find use. The polymers will be condensation polymers. The polymers may be cross-linked or non-cross-linked. Of particular interest are polymers of hydroxyaliphatic carboxylic acids, either homo- or copolymers, and polysaccharides. Included among the polyesters of interest are polymers of D-lactic acid, L-lactic acid, racemic lactic acid, glycolic acid, polycaprolactone, and combinations thereof. By employing the L-lactate or D-lactate, a slowly biodegrading polymer is achieved, while degradation is substantially enhanced with the racemate. Copolymers of glycolic and lactic acid are of particular interest, where the rate of biodegradation is controlled by the ratio of glycolic to lactic acid. The most rapidly degraded copolymer has roughly equal amounts of glycolic and lactic acid, where either homopolymer is more resistant to degradation. The ratio of glycolic acid to lactic acid will also affect the brittleness of in the implant, where a more flexible implant is desirable for larger geometries. Among the polysaccharides of interest are calcium alginate, and functionalized celluloses, particularly carboxymethylcellulose esters characterized by being water insoluble, a molecular weight of about 5 kD to 500 kD, *etc.* Biodegradable hydrogels may also be employed in the implants of the subject invention. Hydrogels are typically a copolymer material, characterized by the ability to imbibe a liquid. Exemplary biodegradable hydrogels which may be employed are described in Heller in: Hydrogels in Medicine and Pharmacy, N. A. Peppes ed., Vol. III, CRC Press, Boca Raton, Fla., 1987, pp 137-149.

Pharmaceutical dosages

[0341] Pharmaceutical compositions of the present disclosure containing an anti-TREM2 antibody of the present disclosure may be administered to an individual in need of treatment with the anti-TREM2 antibody, preferably a human, in accord with known methods, such as intravenous administration as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerobrospinal, intracranial, intraspinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes.

[0342] Dosages and desired drug concentration of pharmaceutical compositions of the present disclosure may vary depending on the particular use envisioned. The determination of the appropriate dosage or route of administration is well within the skill of an ordinary artisan. Animal experiments provide reliable guidance for the determination of effective doses for human therapy. Interspecies scaling of effective doses can be performed following the principles described in Mordenti, J. and Chappell, W. "The Use of Interspecies Scaling in Toxicokinetics," In *Toxicokinetics and New Drug Development*, Yacobi et al., Eds, Pergamon Press, New York 1989, pp.42-46.

[0343] For *in vivo* administration of any of the anti-TREM2 antibodies of the present disclosure, normal dosage amounts may vary from about 10 ng/kg up to about 100 mg/kg of an individual's body weight or more per day, preferably about 1 mg/kg/day to 10 mg/kg/day, depending upon the route of administration. For repeated administrations over several days or longer, depending on the severity of the disease, disorder, or condition to be treated, the treatment is sustained until a desired suppression of symptoms is achieved.

[0344] An exemplary dosing regimen may include administering an initial dose of an anti-TREM2 antibody, of about 2 mg/kg, followed by a weekly maintenance dose of about 1 mg/kg every other week. Other dosage regimens may be useful, depending on the pattern of pharmacokinetic decay that the physician wishes to achieve. For example, dosing an individual from one to twenty-one times a week is contemplated herein. In certain embodiments, dosing ranging from about 3 μg/kg to about 2 mg/kg (such as about 3 μg/kg, about 10 μg/kg, about 30 μg/kg, about 100 μg/kg, about 300 μg/kg, about 1 mg/kg, and about 2/mg/kg) may be used. In certain embodiments, dosing frequency is three times per day, twice per day, once per day, once every other day, once weekly, once every two weeks, once every four weeks, once every five weeks, once every six weeks, once every seven weeks, once every eight weeks, once every nine weeks, once every ten weeks, or once monthly, once every two months, once every three months, or longer. Progress of the therapy is easily monitored by conventional techniques and assays. The dosing regimen, including the anti-TREM2 antibody administered, can vary over time independently of the dose used.

[0345] Dosages for a particular anti-TREM2 antibody may be determined empirically in individuals who have been given one or more administrations of the anti-TREM2 antibody. Individuals are given incremental doses of an anti-TREM2 antibody. To assess efficacy of an anti-TREM2 antibody, a clinical symptom of any of the diseases, disorders, or conditions of the present disclosure (*e.g.*, dementia, frontotemporal dementia, Alzheimer's disease, Nasu-Hakola disease, and multiple sclerosis) can be monitored.

[0346] Administration of an anti-TREM2 antibody of the present disclosure can be continuous or intermittent, depending, for example, on the recipient's physiological condition, whether the purpose of the administration is therapeutic or prophylactic, and other factors known to skilled practitioners. The administration of an anti-TREM2 antibody may be essentially continuous over a preselected period of time or may be in a series of spaced doses.

[0347] Guidance regarding particular dosages and methods of delivery is provided in the literature; see, for example, U.S. Patent Nos. 4,657,760; 5,206,344; or 5,225,212. It is within the scope of the present disclosure that different formulations will be effective for different treatments and different disorders, and that administration intended to treat a specific organ or tissue may necessitate delivery in a manner different from that to another organ or tissue. Moreover, dosages may be administered by one or more separate administrations, or by continuous infusion. For repeated administrations over several days or longer, depending on the condition, the treatment is sustained

until a desired suppression of disease symptoms occurs. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays.

Therapeutic uses

[0348] As disclosed herein, anti-TREM2 antibodies of the present disclosure may be used for preventing, reducing risk, or treating dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, tauopathy disease, Nasu-Hakola disease, stroke, acute trauma, chronic trauma, cognitive deficit, memory loss, lupus, acute and chronic colitis, rheumatoid arthritis, wound healing, Crohn's disease, inflammatory bowel disease, ulcerative colitis, obesity, malaria, essential tremor, central nervous system lupus, Behcet's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, Shy-Drager syndrome, progressive supranuclear palsy, cortical basal ganglionic degeneration, acute disseminated encephalomyelitis, granulomartous disorders, sarcoidosis, diseases of aging, seizures, spinal cord injury, traumatic brain injury, age related macular degeneration, glaucoma, retinitis pigmentosa, retinal degeneration, respiratory tract infection, sepsis, eye infection, systemic infection, lupus, arthritis, multiple sclerosis, low bone density, osteoporosis, osteogenesis, osteopetrotic disease, Paget's disease of bone, cancer, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, polycythemia vera, essential thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express TREM2, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and/or Haemophilus influenza. In some embodiments, the anti-TREM2 antibodies are agonist antibodies.

[0349] In some embodiments, the present disclosure provides methods of preventing, reducing risk, or treating an individual having dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, tauopathy disease, Nasu-Hakola disease, stroke, acute trauma, chronic trauma, cognitive deficit, memory loss, lupus, acute and chronic colitis, rheumatoid arthritis, wound healing, Crohn's disease, inflammatory bowel disease, ulcerative colitis, obesity, malaria, essential tremor, central nervous system lupus, Behcet's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, Shy-Drager syndrome, progressive supranuclear palsy, cortical basal ganglionic degeneration, acute disseminated encephalomyelitis,

granulomartous disorders, sarcoidosis, diseases of aging, seizures, spinal cord injury, traumatic brain injury, age related macular degeneration, glaucoma, retinitis pigmentosa, retinal degeneration, respiratory tract infection, sepsis, eye infection, systemic infection, lupus, arthritis, multiple sclerosis, low bone density, osteoporosis, osteogenesis, osteopetrotic disease, Paget's disease of bone, cancer, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, polycythemia vera, essential thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myelosclerosis, myeloid-derived tumors, tumors that express TREM2, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningiditis* infection, type I HIV, and Haemophilus influenza, by administering to the individual a therapeutically effective amount of an anti-TREM2 antibody of the present disclosure. In some embodiments, the method further includes administering to the individual at least one antibody that specifically binds to an inhibitory checkpoint molecule, and/or another standard or investigational anti-cancer therapy. In some embodiments, the antibody that specifically binds to an inhibitory checkpoint molecule is administered in combination with the isolated antibody. In some embodiments, the at least one antibody that specifically binds to an inhibitory checkpoint molecule is selected from an anti-PD-L1 antibody, an anti-CTLA-4 antibody, an anti-PD-L2 antibody, an anti-PD-1 antibody, an anti-B7-H3 antibody, an anti-B7-H4 antibody, and anti-HVEM antibody, an anti- B- and T-lymphocyte attenuator (BTLA) antibody, an anti-Killer inhibitory receptor (KIR) antibody, an anti-GAL9 antibody, an anti-TIM3 antibody, an anti-A2AR antibody, an anti-LAG-3 antibody, an anti-phosphatidylserine antibody, an anti-CD27 antibody, and any combination thereof. In some embodiments, the standard or investigational anti-cancer therapy is one or more therapies selected from radiotherapy, cytotoxic chemotherapy, targeted therapy, hormonal therapy, imatinib (Gleevec®), trastuzumab (Herceptin®), bevacizumab (Avastin®), Ofatumumab (Arzerra®), Rituximab (Rituxan®, MabThera®, Zytux®), cryotherapy, ablation, radiofrequency ablation, adoptive cell transfer (ACT), chimeric antigen receptor T cell transfer (CAR-T), vaccine therapy, and cytokine therapy. In some embodiments, the method further includes administering to the individual at least one antibody that specifically binds to an inhibitory cytokine. In some embodiments, the at least one antibody that specifically binds to an inhibitory cytokine is administered in combination with the isolated antibody. In some embodiments, the at least one antibody that specifically binds to an inhibitory cytokine is selected from an anti-CCL2 antibody, an anti-CSF-1 antibody, an anti-IL-2 antibody, and any combination thereof. In some embodiments, the method further includes administering to the individual at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein. In some embodiments, the at least

one agonistic antibody that specifically binds to a stimulatory checkpoint protein is administered in combination with the isolated antibody. In some embodiments, the at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein is selected from an agonist anti-CD40 antibody, an agonist anti-OX40 antibody, an agonist anti-ICOS antibody, an agonist anti-CD28 antibody, an agonist anti-CD137/4-1BB antibody, an agonist anti-CD27 antibody, an agonist anti-glucocorticoid-induced TNFR-related protein GITR antibody, and any combination thereof. In some embodiments, the method further includes administering to the individual at least one stimulatory cytokine. In some embodiments, the at least one stimulatory cytokine is administered in combination with the isolated antibody. In some embodiments, the at least one stimulatory cytokine is selected from TNF-α, IL-10, IL-6, IL-8, CRP, TGF-beta members of the chemokine protein families, IL20 family member, IL-33, LIF, OSM, CNTF, TGF-beta, IL-11, IL-12, IL-17, IL-8, IL-23, IFN-α, IFN-β, IL-2, IL-18, GM-CSF, G-CSF, and any combination thereof.

[0350] In some embodiments, the present disclosure provides methods of preventing, reducing risk, or treating an individual having Alzheimer's disease by administering to the individual a therapeutically effective amount of an anti-TREM2 antibody of the present disclosure. In some embodiments, the anti-TREM2 antibody increases expression of one or more inflammatory mediators, such as IL-1β, TNF-α, YM-1, CD86, CCL2, CCL3, CCL5, CCR2, CXCL10, Gata3, Rorc, and any combination thereof. In some embodiments, the anti-TREM2 antibody decreases expression of one or more inflammatory mediators, such as FLT1, OPN, CSF-1, CD11c, AXL, and any combination thereof. In some embodiments, the anti-TREM2 antibody decreases levels of Abeta peptide in the individual (*e.g.*, in the brain of the individual). In some embodiments, the anti-TREM2 antibody increases the number of $CD11b^+$ microglial cells in the brain of the individual. In some embodiments, the anti-TREM2 antibody increases memory in the individual. In some embodiments, the anti-TREM2 antibody reduces cognitive deficit in the individual. In some embodiments, the anti-TREM2 antibody increases motor coordination in the individual.

[0351] In some embodiments, the present disclosure provides methods of increasing memory, reducing cognitive deficit, or both in an individual in need thereof, by administering to the individual a therapeutically effective amount of an anti-TREM2 antibody of the present disclosure.

[0352] In some embodiments, the present disclosure provides methods of increasing motor coordination in an individual in need thereof, by administering to the individual a therapeutically effective amount of an anti-TREM2 antibody of the present disclosure.

[0353] In some embodiments, the present disclosure provides methods of reducing Abeta peptide levels in an individual in need thereof, by administering to the individual a therapeutically effective amount of an anti-TREM2 antibody of the present disclosure.

[0354] In some embodiments, the present disclosure provides methods of increasing the number of $CD11b^+$ microglial cells in an individual in need thereof, by administering to the individual a therapeutically effective amount of an anti-TREM2 antibody of the present disclosure.

[0355] In some embodiments, the present disclosure provides methods of increasing levels of one or more of FLT1, OPNCSF1, CD11c, and AXL in an individual in need thereof, by administering to the individual a therapeutically effective amount of an anti-TREM2 antibody of the present disclosure.

[0356] In some embodiments, an anti-TREM2 antibody of the present disclosure may increases expression of one or more inflammatory mediators, such as IL-1β, TNF-α, YM-1, CD86, CCL2, CCL3, CCL5, CCR2, CXCL10, Gata3, Rorc, and any combination thereof in one or more cells of an individual by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 160%, at least 170%, at least 180%, at least 190%, or at least 200% for example, as compared to expression of one or more inflammatory mediators, such as IL-1β, TNF-α, YM-1, CD86, CCL2, CCL3, CCL5, CCR2, CXCL10, Gata3, Rorc, and any combination thereof in one or more cells of a corresponding individual that is not treated with the anti-TREM2 antibody. In other embodiments, an anti-TREM2 antibody of the present disclosure increases expression of one or more inflammatory mediators, such as IL-1β, TNF-α, YM-1, CD86, CCL2, CCL3, CCL5, CCR2, CXCL10, Gata3, Rorc, and any combination thereof in one or more cells of an individual by at least 1.5 fold, at least 1.6 fold, at least 1.7 fold, at least 1.8 fold, at least 1.9 fold, at least 2.0 fold, at least 2.1 fold, at least 2.15 fold, at least 2.2 fold, at least 2.25 fold, at least 2.3 fold, at least 2.35 fold, at least 2.4 fold, at least 2.45 fold, at least 2.5 fold, at least 2.55 fold, at least 3.0 fold, at least 3.5 fold, at least 4.0 fold, at least 4.5 fold, at least 5.0 fold, at least 5.5 fold, at least 6.0 fold, at least 6.5 fold, at least 7.0 fold, at least 7.5 fold, at least 8.0 fold, at least 8.5 fold, at least 9.0 fold, at least 9.5 fold, or at least 10 fold, for example, as compared to expression of one or more inflammatory mediators, such as IL-1β, TNF-α, YM-1, CD86, CCL2, CCL3, CCL5, CCR2, CXCL10, Gata3, Rorc, and any combination thereof in one or more cells of a corresponding individual that is not treated with the anti-TREM2 antibody.

[0357] In some embodiments, an anti-TREM2 antibody of the present disclosure may decrease expression of one or more inflammatory mediators, such as FLT1, OPN, CSF-1, CD11c, AXL, and any combination thereof in one or more cells of an individual by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 160%, at least 170%, at least 180%, at least 190%, or at least 200% for example, as compared to expression of one or more inflammatory mediators, such as FLT1, OPN, CSF-1, CD11c, AXL, and any combination thereof in one or more cells of a corresponding individual that is not treated with the anti-TREM2 antibody. In other embodiments, an anti-TREM2 antibody of the present disclosure decreases expression of one or more

inflammatory mediators, such as FLT1, OPN, CSF-1, CD11c, AXL, and any combination thereof in one or more cells of an individual by at least 1.5 fold, at least 1.6 fold, at least 1.7 fold, at least 1.8 fold, at least 1.9 fold, at least 2.0 fold, at least 2.1 fold, at least 2.15 fold, at least 2.2 fold, at least 2.25 fold, at least 2.3 fold, at least 2.35 fold, at least 2.4 fold, at least 2.45 fold, at least 2.5 fold, at least 2.55 fold, at least 3.0 fold, at least 3.5 fold, at least 4.0 fold, at least 4.5 fold, at least 5.0 fold, at least 5.5 fold, at least 6.0 fold, at least 6.5 fold, at least 7.0 fold, at least 7.5 fold, at least 8.0 fold, at least 8.5 fold, at least 9.0 fold, at least 9.5 fold, or at least 10 fold, for example, as compared to expression of one or more inflammatory mediators, such as FLT1, OPN, CSF-1, CD11c, AXL, and any combination thereof in one or more cells of a corresponding individual that is not treated with the anti-TREM2 antibody.

[0358] In some embodiments, an anti-TREM2 antibody of the present disclosure may modulate expression of one or more Stage 2 microglia type associated with neurodegenerative diseases (DAM) markers, such as Trem2, Cst7, Ctsl, Lpl, Cd9, Axl, Csf1, Ccl6, Itgax, Clec7a, Lilrb4, Timp2, and any combination thereof in one or more cells of an individual by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 160%, at least 170%, at least 180%, at least 190%, or at least 200% for example, as compared to expression of one or more DAM markers, such as Trem2, Cst7, Ctsl, Lpl, Cd9, Axl, Csf1, Ccl6, Itgax, Clec7a, Lilrb4, Timp2, and any combination thereof in one or more cells of a corresponding individual that is not treated with the anti-TREM2 antibody. *See* Keren-Shaul et al. Cell 169:1276-1290 (2017), which is incorporated by reference in its entirety. In other embodiments, an anti-TREM2 antibody of the present disclosure modulate expression of one or more DAM markers, such as Trem2, Cst7, Ctsl, Lpl, Cd9, Axl, Csf1, Ccl6, Itgax, Clec7a, Lilrb4, Timp2, and any combination thereof in one or more cells of an individual by at least 1.5 fold, at least 1.6 fold, at least 1.7 fold, at least 1.8 fold, at least 1.9 fold, at least 2.0 fold, at least 2.1 fold, at least 2.15 fold, at least 2.2 fold, at least 2.25 fold, at least 2.3 fold, at least 2.35 fold, at least 2.4 fold, at least 2.45 fold, at least 2.5 fold, at least 2.55 fold, at least 3.0 fold, at least 3.5 fold, at least 4.0 fold, at least 4.5 fold, at least 5.0 fold, at least 5.5 fold, at least 6.0 fold, at least 6.5 fold, at least 7.0 fold, at least 7.5 fold, at least 8.0 fold, at least 8.5 fold, at least 9.0 fold, at least 9.5 fold, or at least 10 fold, for example, as compared to expression of one or more DAM markers, such as Trem2, Cst7, Ctsl, Lpl, Cd9, Axl, Csf1, Ccl6, Itgax, Clec7a, Lilrb4, Timp2, and any combination thereof in one or more cells of a corresponding individual that is not treated with the anti-TREM2 antibody. In some embodiments, the DAM marker is Cst7. In some embodiments, the DAM marker is Ccl6. In some embodiments, the DAM marker is Itgax. In some embodiments, the modulation is increased expression.

[0359] Further provided herein are methods of determining whether an individual is a responder or is a non-responder to an anti-TREM2 antibody treatment which comprises the steps of: (a) measuring the levels of one or more Stage 2 microglia type associated with neurodegenerative diseases (DAM) markers, such as Trem2, Cst7, Ctsl, Lpl, Cd9, Axl, Csf1, Ccl6, Itgax, Clec7a, Lilrb4, Timp2, and any combination thereof in a sample from an individual obtained from said individual before the treatment, (b) measuring the level of one or more Stage 2 microglia type associated with neurodegenerative diseases (DAM) markers, such as Trem2, Cst7, Ctsl, Lpl, Cd9, Axl, Csf1, Ccl6, Itgax, Clec7a, Lilrb4, Timp2, and any combination thereof in a sample from an individual obtained from said at a time point after first treatment, and (c) comparing the levels measured at step ii) with the levels measured at step i) wherein a difference between said levels is indicative that said individual is a responder or non-responder. In some embodiments, the difference between said levels is an increase and is indicative that said individual is a responder. In some embodiments, the difference between said levels is a decrease or no change and is indicative that said individual is a non-responder. In some embodiments, the DAM marker is Cst7. In some embodiments, the DAM marker is Ccl6. In some embodiments, the DAM marker is Itgax.

[0360] In some embodiments, an anti-TREM2 antibody of the present disclosure may decrease levels of Abeta peptide in one or more cells of an individual by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 160%, at least 170%, at least 180%, at least 190%, or at least 200% for example, as compared to levels of Abeta peptide in one or more cells of a corresponding individual that is not treated with the anti-TREM2 antibody. In other embodiments, an anti-TREM2 antibody of the present disclosure decreases levels of Abeta peptide in one or more cells of an individual by at least 1.5 fold, at least 1.6 fold, at least 1.7 fold, at least 1.8 fold, at least 1.9 fold, at least 2.0 fold, at least 2.1 fold, at least 2.15 fold, at least 2.2 fold, at least 2.25 fold, at least 2.3 fold, at least 2.35 fold, at least 2.4 fold, at least 2.45 fold, at least 2.5 fold, at least 2.55 fold, at least 3.0 fold, at least 3.5 fold, at least 4.0 fold, at least 4.5 fold, at least 5.0 fold, at least 5.5 fold, at least 6.0 fold, at least 6.5 fold, at least 7.0 fold, at least 7.5 fold, at least 8.0 fold, at least 8.5 fold, at least 9.0 fold, at least 9.5 fold, or at least 10 fold, for example, as compared to levels of Abeta peptide in one or more cells of a corresponding individual that is not treated with the anti-TREM2 antibody.

[0361] In some embodiments, an anti-TREM2 antibody of the present disclosure may increase memory of an individual by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 160%, at least 170%, at least 180%, at least 190%, or at least 200% for

example, as compared to the memory of a corresponding individual that is not treated with the anti-TREM2 antibody. In other embodiments, an anti-TREM2 antibody of the present disclosure increases memory of an individual by at least 1.5 fold, at least 1.6 fold, at least 1.7 fold, at least 1.8 fold, at least 1.9 fold, at least 2.0 fold, at least 2.1 fold, at least 2.15 fold, at least 2.2 fold, at least 2.25 fold, at least 2.3 fold, at least 2.35 fold, at least 2.4 fold, at least 2.45 fold, at least 2.5 fold, at least 2.55 fold, at least 3.0 fold, at least 3.5 fold, at least 4.0 fold, at least 4.5 fold, at least 5.0 fold, at least 5.5 fold, at least 6.0 fold, at least 6.5 fold, at least 7.0 fold, at least 7.5 fold, at least 8.0 fold, at least 8.5 fold, at least 9.0 fold, at least 9.5 fold, or at least 10 fold, for example, as compared to the memory of a corresponding individual that is not treated with the anti-TREM2 antibody.

[0362] In some embodiments, an anti-TREM2 antibody of the present disclosure may reduce cognitive deficit in an individual by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 160%, at least 170%, at least 180%, at least 190%, or at least 200% for example, as compared to cognitive deficit in a corresponding individual that is not treated with the anti-TREM2 antibody. In other embodiments, an anti-TREM2 antibody of the present disclosure reduces cognitive deficit an individual by at least 1.5 fold, at least 1.6 fold, at least 1.7 fold, at least 1.8 fold, at least 1.9 fold, at least 2.0 fold, at least 2.1 fold, at least 2.15 fold, at least 2.2 fold, at least 2.25 fold, at least 2.3 fold, at least 2.35 fold, at least 2.4 fold, at least 2.45 fold, at least 2.5 fold, at least 2.55 fold, at least 3.0 fold, at least 3.5 fold, at least 4.0 fold, at least 4.5 fold, at least 5.0 fold, at least 5.5 fold, at least 6.0 fold, at least 6.5 fold, at least 7.0 fold, at least 7.5 fold, at least 8.0 fold, at least 8.5 fold, at least 9.0 fold, at least 9.5 fold, or at least 10 fold, for example, as compared to cognitive deficit in a corresponding individual that is not treated with the anti-TREM2 antibody.

[0363] In some embodiments, an anti-TREM2 antibody of the present disclosure may increase motor coordination in an individual by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 160%, at least 170%, at least 180%, at least 190%, or at least 200% for example, as compared to motor coordination in a corresponding individual that is not treated with the anti-TREM2 antibody. In other embodiments, an anti-TREM2 antibody of the present disclosure increases motor coordination an individual by at least 1.5 fold, at least 1.6 fold, at least 1.7 fold, at least 1.8 fold, at least 1.9 fold, at least 2.0 fold, at least 2.1 fold, at least 2.15 fold, at least 2.2 fold, at least 2.25 fold, at least 2.3 fold, at least 2.35 fold, at least 2.4 fold, at least 2.45 fold, at least 2.5 fold, at least 2.55 fold, at least 3.0 fold, at least 3.5 fold, at least 4.0 fold, at least 4.5 fold, at least 5.0 fold, at least 5.5 fold, at least 6.0 fold, at least 6.5 fold, at least 7.0 fold, at least 7.5 fold, at least 8.0 fold, at

least 8.5 fold, at least 9.0 fold, at least 9.5 fold, or at least 10 fold, for example, as compared to motor coordination in a corresponding individual that is not treated with the anti-TREM2 antibody.

[0364] Other aspects of the present disclosure relate to methods of enhancing one or more TREM2 activities induced by binding of one or more TREM2 ligands to a TREM2 protein in an individual in need thereof, by administering to the individual a therapeutically effective amount of an anti-TREM2 antibody of the present disclosure. Other aspects of the present disclosure relate to methods of inducing one or more TREM2 activities in an individual in need thereof, by administering to the individual a therapeutically effective amount of an anti-TREM2 antibody of the present disclosure. Any suitable method for measuring TREM2 activity, such as the *in vitro* cell-based assays or *in vivo* models of the present disclosure may be used. Exemplary TREM2 activities include, without limitation, TREM2 binding to DAP12; TREM2 phosphorylation; DAP12 phosphorylation; activation of one or more tyrosine kinases, optionally where the one or more tyrosine kinases comprise a Syk kinase, ZAP70 kinase, or both; activation of phosphatidylinositol 3-kinase (PI3K); activation of protein kinase B (Akt); recruitment of phospholipase C-gamma (PLC-gamma) to a cellular plasma membrane, activation of PLC-gamma, or both; recruitment of TEC-family kinase dVav to a cellular plasma membrane; activation of nuclear factor-rB (NF-rB); inhibition of MAPK signaling; phosphorylation of linker for activation of T cells (LAT), linker for activation of B cells (LAB), or both; activation of IL-2-induced tyrosine kinase (Itk); transient activation followed by inhibition of one or more pro-inflammatory mediators selected from IFN-a4, IFN-b, IL-1β, TNF-α, IL-10, IL-6, IL-8, CRP, TGF-beta members of the chemokine protein families, IL-20 family members, IL-33, LIF, IFN-gamma, OSM, CNTF, TGF-beta, GM-CSF, IL-11, IL-12, IL-17, IL-18, IL-23, CXCL10, VEGF, CCL4, and MCP-1, optionally where the transient activation followed by inhibition occur in one or more cells selected from macrophages, M1 macrophages, activated M1 macrophages, M2 macrophages, dendritic cells, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, and microglial cells; phosphorylation of extracellular signal-regulated kinase (ERK); increased expression of C-C chemokine receptor 7 (CCR7) in one or more cells selected from macrophages, M1 macrophages, activated M1 macrophages, M2 macrophages, dendritic cells, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, microglia, M1 microglia, activated M1 microglia, and M2 microglia, and any combination thereof; induction of microglial cell chemotaxis toward CCL19 and CCL21 expressing cells; normalization of disrupted TREM2/DAP12-dependent gene expression; recruitment of Syk, ZAP70, or both to a DAP12/TREM2 complex; increasing activity of one or more TREM2-dependent genes, optionally where the one or more TREM2-dependent genes comprise nuclear factor of activated T-cells (NFAT) transcription factors; increased maturation of dendritic cells, monocytes, microglia, M1 microglia, activated M1 microglia, and M2 microglia, macrophages, M1 macrophages, activated M1 macrophages, M2 macrophages, or any combination thereof; increased ability of dendritic cells, monocytes, microglia, M1 microglia, activated M1 microglia, and M2 microglia, macrophages, M1 macrophages, activated M1

macrophages, M2 macrophages, or any combination thereof to induce T-cell proliferation; enhanced ability, normalized ability, or both of bone marrow-derived dendritic cells to induce antigen-specific T-cell proliferation; induction of osteoclast production, increased rate of osteoclastogenesis, or both; increased survival of dendritic cells, macrophages, M1 macrophages, activated M1 macrophages, M2 macrophages, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, microglia, M1 microglia, activated M1 microglia, and M2 microglia, or any combination thereof; increasing the function of dendritic cells, macrophages, M1 macrophages, activated M1 macrophages, M2 macrophages, microglia, M1 microglia, activated M1 microglia, and M2 microglia, or any combination thereof; modulating phagocytosis by dendritic cells, macrophages, M1 macrophages, activated M1 macrophages, M2 macrophages, monocytes, microglia, M1 microglia, activated M1 microglia, and M2 microglia, or any combination thereof; induction of one or more types of clearance selected from apoptotic neuron clearance, nerve tissue debris clearance, non-nerve tissue debris clearance, bacteria or other foreign body clearance, disease-causing agent clearance, tumor cell clearance, or any combination thereof, optionally where the disease-causing agent is selected from amyloid beta or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, 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, and Repeat-associated non-ATG (RAN) translation products including DiPeptide Repeats,(DPRs peptides) composed of glycine-alanine (GA), glycine-proline (GP), glycine-arginine (GR), proline-alanine (PA), or proline-arginine (PR), antisense GGCCCC (G2C4) repeat-expansion RNA; induction of phagocytosis of one or more of apoptotic neurons, nerve tissue debris, non-nerve tissue debris, bacteria, other foreign bodies, disease-causing agents, tumor cells, or any combination thereof, optionally where the disease-causing agent is selected from amyloid beta or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, 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, and Repeat-associated non-ATG (RAN) translation products including DiPeptide Repeats,(DPRs peptides) composed of glycine-alanine (GA), glycine-proline (GP), glycine-arginine (GR), proline-alanine (PA), or proline-arginine (PR), antisense GGCCCC (G2C4) repeat-expansion RNA; increased expression of one or more stimulatory molecules selected from CD83, CD86 MHC class II, CD40, and any combination thereof, optionally where the CD40 is expressed on dendritic cells, monocytes, macrophages, or any combination thereof, and optionally where the dendritic cells comprise bone marrow-derived dendritic cells; reduced secretion of one or more inflammatory mediators, optionally where the one or more inflammatory mediators are selected from CD86, IFN-a4, IFN-b, IL-1β, TNF-α, IL-10, IL-6, IL-8, CRP, TGF-beta members of the chemokine protein

families, IL-20 family members, IL-33, LIF, IFN-gamma, OSM, CNTF, TGF-beta, GM-CSF, IL-11, IL-12, IL-17, IL-18, IL-23, CXCL10, VEGF, CCL4, and MCP-1, and any combination thereof; increased memory; and reduced cognitive deficit.

[0365] As disclosed herein, anti-TREM2 antibodies of the present disclosure may be used for decreasing cellular levels of TREM2 on one or more cells, including without limitation, dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, macrophages, neutrophils, NK cells, osteoclasts, Langerhans cells of skin, and Kupffer cells and/or cell lines. In some embodiments, the present disclosure provides methods of decreasing cellular levels of TREM2 on one or more cells in an individual in need thereof, by administering to the individual a therapeutically effective amount of an anti-TREM2 antibody of the present disclosure. In some embodiments, the one or more cells are selected from dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, macrophages, neutrophils, NK cells, osteoclasts, Langerhans cells of skin, and Kupffer cells, and any combination thereof. Cellular levels of TREM2 may refer to, without limitation, cell surface levels of TREM2, intracellular levels of TREM2, and total levels of TREM2. In some embodiments, a decrease in cellular levels of TREM2 comprises decrease in cell surface levels of TREM2. As used herein, cell surface levels of TREM2 may be measured by any *in vitro* cell-based assays or suitable *in vivo* model described herein or known in the art. In some embodiments, a decrease in cellular levels of TREM2 comprises a decrease in intracellular levels of TREM2. As used herein, intracellular levels of TREM2 may be measured by any *in vitro* cell-based assays or suitable *in vivo* model described herein or known in the art. In some embodiments, a decrease in cellular levels of TREM2 comprises a decrease in total levels of TREM2. As used herein, total levels of TREM2 may be measured by any *in vitro* cell-based assays or suitable *in vivo* model described herein or known in the art. In some embodiments, the anti-TREM2 antibodies induce TREM2 degradation, TREM2 cleavage, TREM2 internalization, TREM2 shedding, and/or downregulation of TREM2 expression. In some embodiments, cellular levels of TREM2 are measured on primary cells (*e.g.*, dendritic cells, bone marrow-derived dendritic cells, monocytes, microglia, and macrophages) or on cell lines utilizing an *in vitro* cell assay.

[0366] As disclosed herein, anti-TREM2 antibodies of the present disclosure may also be used for increasing memory and/or reducing cognitive deficit. In some embodiments, the present disclosure provides methods of increasing memory and/or reducing cognitive deficit in an individual in need thereof, by administering to the individual a therapeutically effective amount of an anti-TREM2 antibody of the present disclosure.

[0367] In certain embodiments, the individual has a heterozygous TREM2 variant allele having an glutamic acid to stop codon substitution in the nucleic acid sequence encoding amino acid residue 14 of the human TREM2 protein (SEQ ID NO: 1). In certain embodiments, the individual has a heterozygous TREM2 variant allele having a glutamine to stop codon substitution in the nucleic acid sequence encoding amino acid residue 33 of the human TREM2 protein (SEQ ID NO: 1). In certain

embodiments, the individual has a heterozygous TREM2 variant allele having a tryptophan to stop codon substitution in the nucleic acid sequence encoding amino acid residue 44 of the human TREM2 protein (SEQ ID NO: 1). In certain embodiments, the individual has a heterozygous TREM2 variant allele having an arginine to histidine amino acid substitution at amino acid residue 47 of the human TREM2 protein (SEQ ID NO: 1). In certain embodiments, the individual has a heterozygous TREM2 variant allele having a tryptophan to stop codon substitution in the nucleic acid sequence encoding amino acid residue 78 of the human TREM2 protein (SEQ ID NO: 1). In certain embodiments, the individual has a heterozygous TREM2 variant allele having a valine to glycine amino acid substitution at an amino acid corresponding to amino acid residue 126 of the human TREM2 protein (SEQ ID NO: 1). In certain embodiments, the individual has a heterozygous TREM2 variant allele having an aspartic acid to glycine amino acid substitution at an amino acid corresponding to amino acid residue 134 of the human TREM2 protein (SEQ ID NO: 1). In certain embodiments, the individual has a heterozygous TREM2 variant allele having a lysine to asparagine amino acid substitution at an amino acid corresponding to amino acid residue 186 of the human TREM2 protein (SEQ ID NO: 1).

[0368] In some embodiments, the individual has a heterozygous TREM2 variant allele having a guanine nucleotide deletion at a nucleotide corresponding to nucleotide residue G313 of the nucleic acid sequence encoding SEQ ID NO: 1; a guanine nucleotide deletion at a nucleotide corresponding to nucleotide residue G267 of the nucleic acid sequence encoding SEQ ID NO: 1; a threonine to methionine amino acid substitution at an amino acid corresponding to amino acid residue Thr66 of SEQ ID NO: 1; and/or a serine to cysteine amino acid substitution at an amino acid corresponding to amino acid residue Ser116 of SEQ ID NO: 1.

[0369] As disclosed herein, anti-TREM2 antibodies of the present disclosure may also be used for inducing and/or promoting innate immune cell survival. In some embodiments, the present disclosure provides methods of inducing or promoting innate immune cell survival in an individual in need thereof, by administering to the individual a therapeutically effective amount of an anti-TREM2 antibody of the present disclosure.

[0370] As disclosed herein, anti-TREM2 antibodies of the present disclosure may also be used for inducing and/or promoting wound healing, such as after injury. In some embodiments, the wound healing may be colonic wound repair following injury. In some embodiments, the present disclosure provides methods of inducing or promoting wound healing an individual in need thereof, by administering to the individual a therapeutically effective amount of an anti-TREM2 antibody of the present disclosure.

[0371] In some embodiments, the methods of the present disclosure may involve the coadministration of anti-TREM2 antibodies, or bispecific antibodies with TLR antagonists or with agents neutralizing TLR agonist (*e.g.*, neutralizing cytokine or interleukin antibodies).

[0372] In some embodiments, the methods of the present disclosure may involve the administration of chimeric constructs, including an anti-TREM2 antibody of the present disclosure in conjunction with a TREM2 ligand, such as HSP60.

[0373] In some embodiments, the anti-TREM2 antibodies of the present disclosure do not inhibit the growth of one or more innate immune cells. In some embodiments, the anti-TREM2 antibodies of the present disclosure bind to one or more primary immune cells with a K_D of less than50 nM, less than 45 nM, less than 40 nM, less than 35 nM, less than 30 nM, less than 25 nM, less than 20 nM, less than 15 nM, less than 10 nM, less than 9 nM, less than 8 nM, less than 7 nM, less than 6 nM, less than 5 nM, less than 4 nM, less than 3 nM, less than 2 nM, or less than 1 nM. In some embodiments, an anti-TREM2 antibody of the present disclosure accumulates in the brain, or the cerebrospinal fluid (CSF), or both to an extent that is 1% or more, 2% or more, 3% or more, 4% or more, 5% or more, 6% or more, 7% or more, 8% or more, 9% or more, 10% or more of the concentration of the antibody in the blood.

[0374] In some embodiments, a subject or individual is a mammal. Mammals include, without limitation, domesticated animals (*e.g.*, cows, sheep, cats, dogs, and horses), primates (*e.g.*, humans and non-human primates such as monkeys), rabbits, and rodents (*e.g.*, mice and rats). In some embodiments, the subject or individual is a human.

Dementia

[0375] Dementia is a non-specific syndrome (*i.e.*, a set of signs and symptoms) that presents as a serious loss of global cognitive ability in a previously unimpaired person, beyond what might be expected from normal ageing. Dementia may be static as the result of a unique global brain injury. Alternatively, dementia may be progressive, resulting in long-term decline due to damage or disease in the body. While dementia is much more common in the geriatric population, it can also occur before the age of 65. Cognitive areas affected by dementia include, without limitation, memory, attention span, language, and problem solving. Generally, symptoms must be present for at least six months to before an individual is diagnosed with dementia.

[0376] Exemplary forms of dementia include, without limitation, frontotemporal dementia, Alzheimer's disease, vascular dementia, semantic dementia, and dementia with Lewy bodies.

[0377] In some embodiments, administering an anti-TREM2 antibody of the present disclosure can prevent, reduce the risk, and/or treat dementia. In some embodiments, administering an anti-TREM2 antibody may induce one or more TREM2 activities in an individual having dementia (*e.g.*, DAP12 phosphorylation, PI3K activation, increased expression of one or more anti-inflammatory mediators, or reduced expression of one or more pro-inflammatory mediators).

Frontotemporal dementia

[0378] Frontotemporal dementia (FTD) is a condition resulting from the progressive deterioration of the frontal lobe of the brain. Over time, the degeneration may advance to the temporal

lobe. Second only to Alzheimer's disease (AD) in prevalence, FTD accounts for 20% of pre-senile dementia cases. The clinical features of FTD include memory deficits, behavioral abnormalities, personality changes, and language impairments (Cruts, M. & Van Broeckhoven, C., Trends Genet. 24:186-194 (2008); Neary, D., et al., Neurology 51:1546-1554 (1998); Ratnavalli, E., Brayne, C., Dawson, K. & Hodges, J. R., Neurology 58:1615-1621 (2002)).

[0379] A substantial portion of FTD cases are inherited in an autosomal dominant fashion, but even in one family, symptoms can span a spectrum from FTD with behavioral disturbances, to Primary Progressive Aphasia, to Cortico-Basal Ganglionic Degeneration. FTD, like most neurodegenerative diseases, can be characterized by the pathological presence of specific protein aggregates in the diseased brain. Historically, the first descriptions of FTD recognized the presence of intraneuronal accumulations of hyperphosphorylated Tau protein in neurofibrillary tangles or Pick bodies. A causal role for the microtubule associated protein Tau was supported by the identification of mutations in the gene encoding the Tau protein in several families (Hutton, M., et al., Nature 393:702-705 (1998). However, the majority of FTD brains show no accumulation of hyperphosphorylated Tau but do exhibit immunoreactivity to ubiquitin (Ub) and TAR DNA binding protein (TDP43) (Neumann, M., et al., Arch. Neurol. 64:1388-1394 (2007)). A majority of those FTD cases with Ub inclusions (FTD-U) were shown to carry mutations in the progranulin gene.

[0380] In some embodiments, administering an anti-TREM2 antibody of the present disclosure can prevent, reduce the risk, and/or treat FTD. In some embodiments, administering an anti-TREM2 antibody may induce one or more TREM2 activities in an individual having FTD (*e.g.*, DAP12 phosphorylation, PI3K activation, increased expression of one or more anti-inflammatory mediators, or reduced expression of one or more pro-inflammatory mediators).

Alzheimer's disease

[0381] Alzheimer's disease (AD) is the most common form of dementia. There is no cure for the disease, which worsens as it progresses, and eventually leads to death. Most often, AD is diagnosed in people over 65 years of age. However, the less-prevalent early-onset Alzheimer's can occur much earlier.

[0382] Common symptoms of Alzheimer's disease include, behavioral symptoms, such as difficulty in remembering recent events; cognitive symptoms, confusion, irritability and aggression, mood swings, trouble with language, and long-term memory loss. As the disease progresses bodily functions are lost, ultimately leading to death. Alzheimer's disease develops for an unknown and variable amount of time before becoming fully apparent, and it can progress undiagnosed for years.

[0383] In some embodiments, administering an anti-TREM2 antibody of the present disclosure can prevent, reduce the risk, and/or treat Alzheimer's disease. In some embodiments, administering an anti-TREM2 antibody may induce one or more TREM2 activities in an individual having Alzheimer's

disease (*e.g.*, DAP12 phosphorylation, PI3K activation, increased expression of one or more anti-inflammatory mediators, or reduced expression of one or more pro-inflammatory mediators).

Nasu-Hakola disease

[0384] Nasu-Hakola disease (NHD), which may alternatively be referred to as polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL), is a rare inherited leukodystrophy characterized by progressive presenile dementia associated with recurrent bone fractures due to polycystic osseous lesions of the lower and upper extremities. NHD disease course is generally divided into four stages: latent, osseous, early neurologic, and late neurologic. After a normal development during childhood (latent stage), NHD starts manifesting during adolescence or young adulthood (typical age of onset 20-30 years) with pain in the hands, wrists, ankles, and feet. Patients then start suffering from recurrent bone fractures due to polycystic osseous and osteroporotic lesions in the limb bones (osseous stage). During the third or fourth decade of life (early neurologic stage), patients present with pronounced personality changes (*e.g.*, euphoria, lack of concentration, loss of judgment, and social inhibitions) characteristic of a frontal lobe syndrome. Patients also typically suffer from progressive memory disturbances. Epileptic seizures are also frequently observed. Finally (late neurologic stage), patients progress to a profound dementia, are unable to speak and move, and usually die by the age of 50.

[0385] In some embodiments, administering an anti-TREM2 antibody of the present disclosure can prevent, reduce the risk, and/or treat Nasu-Hakola disease (NHD). In some embodiments, administering an anti-TREM2 antibody may induce one or more TREM2 activities in an individual having NHD (*e.g.*, DAP12 phosphorylation, PI3K activation, increased expression of one or more anti-inflammatory mediators, or reduced expression of one or more pro-inflammatory mediators).

Parkinson's disease

[0386] Parkinson's disease, which may be referred to as idiopathic or primary parkinsonism, hypokinetic rigid syndrome (HRS), or paralysis agitans, is a neurodegenerative brain disorder that affects motor system control. The progressive death of dopamine-producing cells in the brain leads to the major symptoms of Parkinson's. Most often, Parkinson's disease is diagnosed in people over 50 years of age. Parkinson's disease is idiopathic (having no known cause) in most people. However, genetic factors also play a role in the disease.

[0387] Symptoms of Parkinson's disease include, without limitation, tremors of the hands, arms, legs, jaw, and face, muscle rigidity in the limbs and trunk, slowness of movement (bradykinesia), postural instability, difficulty walking, neuropsychiatric problems, changes in speech or behavior, depression, anxiety, pain, psychosis, dementia, hallucinations, and sleep problems.

[0388] In some embodiments, administering an anti-TREM2 antibody of the present disclosure can prevent, reduce the risk, and/or treat Parkinson's disease. In some embodiments, administering an anti-TREM2 antibody may induce one or more TREM2 activities in an individual having Parkinson's

disease (*e.g.*, DAP12 phosphorylation, PI3K activation, increased expression of one or more anti-inflammatory mediators, or reduced expression of one or more pro-inflammatory mediators).

Amyotrophic lateral sclerosis

[0389] As used herein, amyotrophic lateral sclerosis (ALS) or, motor neuron disease or, Lou Gehrig's disease are used interchangeably and refer to a debilitating disease with varied etiology characterized by rapidly progressive weakness, muscle atrophy and fasciculations, muscle spasticity, difficulty speaking (dysarthria), difficulty swallowing (dysphagia), and difficulty breathing (dyspnea).

[0390] It has been shown that progranulin play a role in ALS (Schymick, JC et al., (2007) J Neurol Neurosurg Psychiatry.;78:754-6) and protects again the damage caused by ALS causing proteins such as TDP-43 (Laird, AS et al., (2010). PLoS ONE 5: e13368). It was also demonstrated that pro-NGF induces p75 mediated death of oligodendrocytes and corticospinal neurons following spinal cord injury (Beatty et al., Neuron (2002),36, pp. 375-386; Giehl et al, Proc. Natl. Acad. Sci USA (2004), 101, pp 6226-30).

[0391] In some embodiments, administering an anti-TREM2 antibody of the present disclosure can prevent, reduce the risk, and/or treat ALS. In some embodiments, administering an anti-TREM2 antibody may induce one or more TREM2 activities in an individual having ALS (*e.g.*, DAP12 phosphorylation, PI3K activation, increased expression of one or more anti-inflammatory mediators, or reduced expression of one or more pro-inflammatory mediators).

Huntington's disease

[0392] Huntington's disease (HD) is an inherited neurodegenerative disease caused by an autosomal dominant mutation in the Huntingtin gene (HTT). Expansion of a cytokine-adenine-guanine (CAG) triplet repeat within the Huntingtin gene results in production of a mutant form of the Huntingtin protein (Htt) encoded by the gene. This mutant Huntingtin protein (mHtt) is toxic and contributes to neuronal death. Symptoms of Huntington's disease most commonly appear between the ages of 35 and 44, although they can appear at any age.

[0393] Symptoms of Huntington's disease, include, without limitation, motor control problems, jerky, random movements (chorea), abnormal eye movements, impaired balance, seizures, difficulty chewing, difficulty swallowing, cognitive problems, altered speech, memory deficits, thinking difficulties, insomnia, fatigue, dementia, changes in personality, depression, anxiety, and compulsive behavior.

[0394] In some embodiments, administering an anti-TREM2 antibody of the present disclosure can prevent, reduce the risk, and/or treat Huntington's disease (HD). In some embodiments, administering an anti-TREM2 antibody may induce one or more TREM2 activities in an individual having HD (*e.g.*, DAP12 phosphorylation, PI3K activation, increased expression of one or more anti-inflammatory mediators, or reduced expression of one or more pro-inflammatory mediators).

Tauopathy disease

[0395] Tauopathy diseases, or Tauopathies, are a class of neurodegenerative disease caused by aggregation of the microtubule-associated protein tau within the brain. Alzheimer's disease (AD) is the most well-known tauopathy disease, and involves an accumulation of tau protein within neurons in the form of insoluble neurofibrillary tangles (NFTs). Other tauopathy diseases and disorders include progressive supranuclear palsy, dementia pugilistica (chromic traumatic encephalopathy), Frontotemporal dementia and parkinsonism linked to chromosome 17, Lytico-Bodig disease (Parkinson-dementia complex of Guam), Tangle-predominant dementia, Ganglioglioma and gangliocytoma, Meningioangiomatosis, Subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, lipofuscinosis, Pick's disease, corticobasal degeneration, Argyrophilic grain disease (AGD), Huntington's disease, frontotemporal dementia, and frontotemporal lobar degeneration.

[0396] In some embodiments, administering an anti-TREM2 antibody of the present disclosure can prevent, reduce the risk, and/or treat tauopathy disease. In some embodiments, administering an anti-TREM2 antibody may induce one or more TREM2 activities in an individual having tauopathy disease (*e.g.*, DAP12 phosphorylation, PI3K activation, increased expression of one or more anti-inflammatory mediators, or reduced expression of one or more pro-inflammatory mediators).

Multiple sclerosis

[0397] Multiple sclerosis (MS) can also be referred to as disseminated sclerosis or encephalomyelitis disseminata. MS is an inflammatory disease in which the fatty myelin sheaths around the axons of the brain and spinal cord are damaged, leading to demyelination and scarring as well as a broad spectrum of signs and symptoms. MS affects the ability of nerve cells in the brain and spinal cord to communicate with each other effectively. Nerve cells communicate by sending electrical signals called action potentials down long fibers called axons, which are contained within an insulating substance called myelin. In MS, the body's own immune system attacks and damages the myelin. When myelin is lost, the axons can no longer effectively conduct signals. MS onset usually occurs in young adults, and is more common in women.

[0398] Symptoms of MS include, without limitation, changes in sensation, such as loss of sensitivity or tingling; pricking or numbness, such as hypoesthesia and paresthesia; muscle weakness; clonus; muscle spasms; difficulty in moving; difficulties with coordination and balance, such as ataxia; problems in speech, such as dysarthria, or in swallowing, such as dysphagia; visual problems, such as nystagmus, optic neuritis including phosphenes, and diplopia; fatigue; acute or chronic pain; and bladder and bowel difficulties; cognitive impairment of varying degrees; emotional symptoms of depression or unstable mood; Uhthoff's phenomenon, which is an exacerbation of extant symptoms due to an exposure to higher than usual ambient temperatures; and Lhermitte's sign, which is an electrical sensation that runs down the back when bending the neck.

[0399] In some embodiments, administering an anti-TREM2 antibody of the present disclosure can prevent, reduce the risk, and/or treat multiple sclerosis. In some embodiments, administering an anti-TREM2 antibody may induce one or more TREM2 activities in an individual having multiple sclerosis (*e.g.*, DAP12 phosphorylation, PI3K activation, increased expression of one or more anti-inflammatory mediators, and reduced expression of one or more pro-inflammatory mediators).

Cancer

[0400] Yet further aspects of the present disclosure provide methods for preventing, reducing risk, or treating an individual having cancer, comprising administering to the individual a therapeutically effective amount of an isolated anti-TREM2 antibody of the present disclosure. Any of the isolated antibodies of the present disclosure may be used in these methods.

[0401] As described above, the tumor microenvironment is known to contain a heterogeneous immune infiltrate, which includes T lymphocytes, macrophages and cells of myeloid/granulocytic lineage. In particular, the presence of M2-macrophages in tumors is associated with poor prognosis. Therapies that reduce the number of these cells in the tumor, such as CSF-1R blocking agents, are showing beneficial effects in preclinical models and early stage clinical studies. It has been shown that TREM2 synergizes with CSF-1 to promote survival of macrophages *in vitro*, and that this effect is particularly prominent in M2-type macrophages, compared to other types of phagocytic cells. A seminal preclinical study has also shown synergies between drugs that target tumor-associated macrophages (*e.g.*, CSF-1/CSF-1R blocking antibodies) and checkpoint blocking antibodies that target T cells, indicating that manipulating both cell types shows efficacy in tumor models where individual therapies are poorly effective (Zhu Y; Cancer Res. 2014 Sep 15; 74(18):5057-69). Therefore, without wishing to be bound by theory, it is thought that blocking TREM2 signaling in tumor associated macrophages may inhibit suppression of the immune response in the tumor microenvironment, resulting in a therapeutic anti-tumor immune response.

[0402] Due to the synergies between TREM2 and CSF-1, and between targeting tumor-associated macrophages and targeting T cells, in some embodiments, the methods for preventing, reducing risk, or treating an individual having cancer further include administering to the individual at least one antibody that specifically binds to an inhibitory checkpoint molecule. Examples of antibodies that specifically bind to an inhibitory checkpoint molecule include, without limitation, an anti-PD-L1 antibody, an anti-CTLA-4 antibody, an anti-PD-L2 antibody, an anti-PD-1 antibody, an anti-B7-H3 antibody, an anti-B7-H4 antibody, and anti-HVEM antibody, an anti-BTLA antibody, an anti- GAL9 antibody, an anti-TIM3 antibody, an anti-A2AR antibody, an anti-LAG-3 antibody, an anti-phosphatidylserine antibody, and any combination thereof. In some embodiments, the at least one antibody that specifically binds to an inhibitory checkpoint molecule is administered in combination with an anti-TREM2 antibody of the present disclosure.

[0403] In some embodiments, a cancer to be prevented or treated by the methods of the present disclosure includes, but is not limited to, squamous cell cancer (*e.g.*, epithelial squamous cell cancer), lung cancer including small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer and gastrointestinal stromal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, cancer of the urinary tract, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, melanoma, superficial spreading melanoma, lentigo maligna melanoma, acral lentiginous melanomas, nodular melanomas, multiple myeloma and B-cell lymphoma; chronic lymphocytic leukemia (CLL); acute lymphoblastic leukemia (ALL); hairy cell leukemia; chronic myeloblastic leukemia; and post-transplant lymphoproliferative disorder (PTLD), as well as abnormal vascular proliferation associated with phakomatoses, edema (such as that associated with brain tumors), Meigs' syndrome, brain, as well as head and neck cancer, and associated metastases. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is selected from non-small cell lung cancer, glioblastoma, neuroblastoma, renal cell carcinoma, bladder cancer, ovarian cancer, melanoma, breast carcinoma, gastric cancer, and hepatocellular carcinoma. In some embodiments, the cancer is triple-negative breast carcinoma. In some embodiments, the cancer may be an early stage cancer or a late stage cancer. In some embodiments, the cancer may be a primary tumor. In some embodiments, the cancer may be a metastatic tumor at a second site derived from any of the above types of cancer.

[0404] In some embodiments, anti-TREM2 antibodies of the present disclosure may be used for preventing, reducing risk, or treating cancer, including, without limitation, bladder cancer breast cancer, colon and rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, and thyroid cancer.

[0405] In some embodiments, the present disclosure provides methods of preventing, reducing risk, or treating an individual having cancer, by administering to the individual a therapeutically effective amount of an anti-TREM2 antibody of the present disclosure.

[0406] In some embodiments, the method further includes administering to the individual at least one antibody that specifically binds to an inhibitory checkpoint molecule, and/or another standard or investigational anti-cancer therapy. In some embodiments, the at least one antibody that specifically binds to an inhibitory checkpoint molecule is administered in combination with the isolated antibody. In some embodiments, the at least one antibody that specifically binds to an inhibitory checkpoint molecule is selected from an anti-PD-L1 antibody, an anti-CTLA-4 antibody, an anti-PD-L2 antibody, an anti-PD-1 antibody, an anti-B7-H3 antibody, an anti-B7-H4 antibody, and anti-HVEM antibody, an anti- B- and T-lymphocyte attenuator (BTLA) antibody, an anti- Killer inhibitory receptor (KIR)

antibody, an anti-GAL9 antibody, an anti-TIM3 antibody, an anti-A2AR antibody, an anti-LAG-3 antibody, an anti-phosphatidylserine antibody, an anti-CD27 antibody, and any combination thereof. In some embodiments, the standard or investigational anti-cancer therapy is one or more therapies selected from radiotherapy, cytotoxic chemotherapy, targeted therapy, imatinib (Gleevec®), trastuzumab (Herceptin®), adoptive cell transfer (ACT), chimeric antigen receptor T cell transfer (CAR-T), vaccine therapy, hormonal therapy, bevacizumab (Avastin®), Ofatumumab (Arzerra®), Rituximab (Rituxan®, MabThera®, Zytux®), cryotherapy, ablation, radiofrequency ablation, and cytokine therapy.

[0407] In some embodiments, the method further includes administering to the individual at least one antibody that specifically binds to an inhibitory cytokine. In some embodiments, the at least one antibody that specifically binds to an inhibitory cytokine is administered in combination with the isolated antibody. In some embodiments, the at least one antibody that specifically binds to an inhibitory cytokine is selected from an anti-CCL2 antibody, an anti-CSF-1 antibody, an anti-IL-2 antibody, and any combination thereof.

[0408] In some embodiments, the method further includes administering to the individual at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein. In some embodiments, the at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein is administered in combination with the isolated antibody. In some embodiments, the at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein is selected from an agonist anti-CD40 antibody, an agonist anti-OX40 antibody, an agonist anti-ICOS antibody, an agonist anti-CD28 antibody, an agonist anti-CD137/4-1BB antibody, an agonist anti-CD27 antibody, an agonist anti- glucocorticoid-induced TNFR-related protein GITR antibody, and any combination thereof.

[0409] In some embodiments, the method further includes administering to the individual at least one stimulatory cytokine. In some embodiments, the at least one stimulatory cytokine is administered in combination with the isolated antibody. In some embodiments, the at least one stimulatory cytokine is selected from TNF-α, IL-1□, IL-1β, IL-10, IL-6, IL-8, CRP, TGF-beta members of the chemokine protein families, IL-20 family members, IL-33, LIF, IFN-gamma, OSM, CNTF, TGF-beta, IL-11, IL-12, IL-17, IL-8, CRP, IFN-α, IFN-β, IL-2, IL-18, IL-23, CXCL10, CCL4, MCP-1, VEGF, GM-CSF, G-CSF, and any combination thereof.

Kits/Articles of Manufacture

[0410] The present disclosure also provides kits containing an isolated antibody of the present disclosure (*e.g.*, an anti-TREM2 antibody described herein), or a functional fragment thereof. Kits of the present disclosure may include one or more containers comprising a purified antibody of the present disclosure. In some embodiments, the kits further include instructions for use in accordance with the methods of this disclosure. In some embodiments, these instructions comprise a description

of administration of the isolated antibody of the present disclosure (*e.g.*, an anti-TREM2 antibody described herein) to prevent, reduce risk, or treat an individual having a disease, disorder, or injury selected from dementia, frontotemporal dementia, Alzheimer's disease, Nasu-Hakola disease, multiple sclerosis, and cancer, according to any methods of this disclosure.

[0411] In some embodiments, the instructions comprise a description of how to detect TREM2, for example in an individual, in a tissue sample, or in a cell. The kit may further comprise a description of selecting an individual suitable for treatment based on identifying whether that individual has the disease and the stage of the disease.

[0412] In some embodiments, the kits may further include another antibody of the present disclosure (*e.g.*, at least one antibody that specifically binds to an inhibitory checkpoint molecule, at least one antibody that specifically binds to an inhibitory cytokine, and/or at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein) and/or at least one stimulatory cytokine. In some embodiments, the kits may further include instructions for using the antibody and/or stimulatory cytokine in combination with an isolated antibody of the present disclosure (*e.g.*, an anti-TREM2 antibody described herein), instructions for using the isolated antibody of the present disclosure in combination with an antibody and/or stimulatory cytokine, or instructions for using an isolated antibody of the present disclosure and an antibody and/or stimulatory cytokine, according to any methods of this disclosure.

[0413] The instructions generally include information as to dosage, dosing schedule, and route of administration for the intended treatment. The containers may be unit doses, bulk packages (*e.g.*, multi-dose packages) or sub-unit doses. Instructions supplied in the kits of the present disclosure are typically written instructions on a label or package insert (*e.g.*, a paper sheet included in the kit), but machine-readable instructions (*e.g.*, instructions carried on a magnetic or optical storage disk) are also acceptable.

[0414] The label or package insert indicates that the composition is used for treating, *e.g.*, a disease of the present disclosure. Instructions may be provided for practicing any of the methods described herein.

[0415] The kits of this disclosure are in suitable packaging. Suitable packaging includes, but is not limited to, vials, bottles, jars, flexible packaging (*e.g.*, sealed Mylar or plastic bags), and the like. Also contemplated are packages for use in combination with a specific device, such as an inhaler, nasal administration device (*e.g.*, an atomizer) or an infusion device such as a minipump. A kit may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The container may also have a sterile access port (*e.g.*, the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is an isolated antibody of the present disclosure (*e.g.*, an anti-TREM2antibody described herein). The container may further comprise a second pharmaceutically active agent.

[0416] Kits may optionally provide additional components such as buffers and interpretive information. Normally, the kit comprises a container and a label or package insert(s) on or associated with the container.

Diagnostic uses

[0417] The isolated antibodies of the present disclosure (*e.g.*, an anti-TREM2 antibody described herein) also have diagnostic utility. This disclosure therefore provides for methods of using the antibodies of this disclosure, or functional fragments thereof, for diagnostic purposes, such as the detection of TREM2 in an individual or in tissue samples derived from an individual.

[0418] In some embodiments, the individual is a human. In some embodiments, the individual is a human patient suffering from, or at risk for developing, cancer. In some embodiments, the diagnostic methods involve detecting TREM2 in a biological sample, such as a biopsy specimen, a tissue, or a cell. An isolated antibody of the present disclosure (*e.g.*, an anti-TREM2 antibody described herein) is contacted with the biological sample and antigen-bound antibody is detected. For example, a tumor sample (*e.g.*, a biopsy specimen) may be stained with an anti-TREM2 antibody described herein in order to detect and/or quantify tumor-associated macrophages (*e.g.*, M2-type macrophages). The detection method may involve quantification of the antigen-bound antibody. Antibody detection in biological samples may occur with any method known in the art, including immunofluorescence microscopy, immunocytochemistry, immunohistochemistry, ELISA, FACS analysis, immunoprecipitation, or micro-positron emission tomography. In certain embodiments, the antibody is radiolabeled, for example with ^{18}F and subsequently detected utilizing micro-positron emission tomography analysis. Antibody-binding may also be quantified in a patient by non-invasive techniques such as positron emission tomography (PET), X-ray computed tomography, single-photon emission computed tomography (SPECT), computed tomography (CT), and computed axial tomography (CAT).

[0419] In other embodiments, an isolated antibody of the present disclosure (*e.g.*, an anti-TREM2 antibody described herein) may be used to detect and/or quantify, for example, microglia in a brain specimen taken from a preclinical disease model (*e.g.*, a non-human disease model). As such, an isolated antibody of the present disclosure (*e.g.*, an anti-TREM2 antibody described herein) may be useful in evaluating therapeutic response after treatment in a model for a nervous system disease or injury such as dementia, frontotemporal dementia, Alzheimer's disease, Nasu-Hakola disease, or multiple sclerosis, as compared to a control.

Antibodies with modified constant regions

[0420] Other aspects of the present disclosure relate to antibodies having modified constant regions (i.e., Fc regions). In some embodiments the modified Fc regions include two or more amino acid substitutions that increase antibody clustering without activating complement as compared to a corresponding antibody having an Fc region that does not include the two or more amino acid

substitutions. Accordingly, in some embodiments, the antibody is an antibody comprising an Fc region, where 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: L234F, L235A, L235E, S267E, K322A, L328F, A330S, P331S, and any combination thereof, where the numbering of the residues is according to EU or Kabat numbering. In some embodiments, the Fc region comprises an amino acid substitution at positions E430G, L243A, L235A, and P331S, where the numbering of the residue position is according to EU numbering. In some embodiments, the Fc region comprises an amino acid substitution at positions E430G and P331S, where the numbering of the residue position is according to EU numbering. In some embodiments, the Fc region comprises an amino acid substitution at positions E430G and K322A, where the numbering of the residue position is according to EU numbering. In some embodiments, the Fc region comprises an amino acid substitution at positions E430G, A330S, and P331S, where the numbering of the residue position is according to EU numbering. In some embodiments, the Fc region comprises an amino acid substitution at positions E430G, K322A, A330S, and P331S, where the numbering of the residue position is according to EU numbering. In some embodiments, the Fc region comprises an amino acid substitution at positions E430G, K322A, and A330S, where the numbering of the residue position is according to EU numbering. In some embodiments, the Fc region comprises an amino acid substitution at positions E430G, K322A, and P331S, where the numbering of the residue position is according to EU numbering.

[0421] In some embodiments, 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 embodiments, the antibody induces one or more activities of a target specifically bound by the antibody. In some embodiments, the antibody binds to TREM2.

[0422] The present disclosure will be more fully understood by reference to the following Examples. They should not, however, be construed as limiting the scope of the present disclosure. All citations throughout the disclosure are hereby expressly incorporated by reference.

EXAMPLES

Example 1: Humanized AL2p antibodies retain affinity and function

[0423] The mouse anti-TREM2 antibody AL2p is also known as 9F5 and 9F5a in WO 2017/062672 (PCT/US2016/055828).

Methods

[0424] Humanized versions of the mouse anti-TREM2 antibody AL2p were generated by combining 21 human IgG1 versions of VH with 6 human IgG1 versions of VK, each containing from 0 to 11 framework residue mutations. These variants were tested by ForteBio for affinity to the TREM2 antigen and 94 variants were chosen for further *in vitro* analysis.

[0425] The affinity of the TREM2 antibodies was determined by measuring their K_D, as well as on- and off-rates by ForteBio OctetRed as previously described by Estep et al., Mabs 2013: 5(2):270-278. Briefly, IgG's were loaded on-line onto AHQ sensors. Sensors were equilibrated off-line in assay buffer for 30 minutes and then monitored on-line for 60 seconds for baseline establishment. For avid binding measurement, sensors with loaded IgGs were exposed to 100 nM antigen (human TREM2 Fc fusion using the entire TREM2 ECD; only one Fc arm was fused to TREM2) for 3 minutes, afterwards they were transferred to assay buffer for 3 minutes for off-rate measurement. Monovalent binding measurements were obtained by loading human TREM2 Fc fusion antigens to AHQ sensor and followed by exposure to ~100 nM TREM2 antibody Fab. Kinetics data were fit using a 1:1 binding model in the data analysis software provided by ForteBio. Assay was run at room temperature (25°C).

[0426] To examine cell binding of anti-TREM2 antibodies, recombinant, human TREM2-expressing BW5147.G.1.4 cells (ATCC® TIB48™) were established by stably expressing either mouse TREM2 or human TREM2 together with Dap12 using viral infection. Cells were harvested by scraping, washed in PBS, counted and plated on 96-well U bottom plates at $1x10^5$ cells/ well. The plates were spun at 1,400 rpm for 3 minutes and primary anti-TREM2 or control antibodies were added in FACS buffer (PBS + 2% FBS) and incubated on ice for one hour. Cells were subsequently centrifuged as before and washed thrice with FACS buffer. Cells were then incubated with anti-human PE conjugated secondary antibody (BD Biosciences) in FACS buffer for 30 minutes on ice. Cells were again washed thrice with FACS buffer and analyzed on a BD FACS Canto. Binding was measured as mean fluorescence intensity in the APC channel.

[0427] The ability of plate-bound full-length anti-TREM2 antibodies to activate human TREM2-dependent genes was evaluated using a luciferase reporter gene under the control of an NFAT (nuclear factor of activated T-cells) promoter. The cell line BW5147.G.1.4, derived from mouse thymus lymphoma T lymphocytes, was infected with a human TREM2/DAP12 fusion protein, and with Cignal Lenti NFAT-Luciferase virus (Qiagen). To test antibodies in solution, they were added to the culture plates together with the cells and incubated for 4 to 6 hours at 37°C. Luciferase activity was measured by adding OneGlo Reagent (Promega) to each well and incubating for 3 minutes at room temperature on a plate shaker. Luciferase signal was measured using a BioTek plate reader.

Results

[0428] Humanized versions of anti-TREM2 antibody AL2p were generated by combining 21 human IgG1 versions of VH with 6 human IgG1 versions of VK, each containing from 0 to 11 framework residue mutations. The heavy chain and light chain variable region sequences of 26 humanized anti-TREM2 antibodies are depicted in **Tables 6 and 7.**

[0429] Clones were tested for affinity to human TREM2 by ForteBio Octet Red (**Table 1**). Most humanized AL2p variants retained a similar affinity as the human mouse AL2p chimeric parental antibody (which has a mouse antibody variable region and a human Fc region). In addition,

humanized variants retained ability to bind to human TREM2 expressed on BW cells, with some even showing an improved affinity over the parental antibody (**Table 1**). Furthermore, humanized variants retained the ability to induce TREM2 signaling in a heterologous NFAT:luciferase signaling assay (**Table 1**). Two variants (AL2p-h50 and AL2p-h77) were chosen to move into affinity maturation as they both retained affinity and function of the parental antibody, while containing few changes from human germline indicating low immunogenicity.

Table 1: Characterization of humanized versions of anti-TREM2 antibody AL2p

Antibody	Fab K_D human TREM2-Fc (M) Monovalent	Cell binding human TREM2/DAP12 BWZ (FOB)	Soluble luciferase activation at 10µg/ml Fold over control
AL2p	1.02E-07	79	3.55
AL2p-h19	1.93E-07	87	4.97
AL2p-h21	1.37E-07	76	6.28
AL2p-h22	3.25E-07	61	5.00
AL2p-h23	3.34E-07	76	5.38
AL2p-h24	1.15E-06	69	4.36
AL2p-h25	1.53E-07	90	7.45
AL2p-h26	9.53E-08	78	7.25
AL2p-h27	1.20E-07	78	7.23
AL2p-h28	N.B.	79	5.59
AL2p-h29	N.B.	82	5.80
AL2p-h30	1.81E-07	88	6.01
AL2p-h31	1.16E-07	83	5.04
AL2p-h32	1.44E-07	81	5.60
AL2p-h33	2.25E-07	74	6.21
AL2p-h34	1.42E-07	84	6.92
AL2p-h35	1.27E-07	69	6.81
AL2p-h36	N.B.	85	4.13
AL2p-h42	1.41E-07	79	9.29
AL2p-h43	1.34E-07	91	8.65
AL2p-h44	1.80E-07	80	7.29
AL2p-h47	1.61E-07	93	9.28
AL2p-h50	1.80E-07	78	6.36
AL2p-h59	1.30E-07	69	7.06
AL2p-h76	8.30E-08	86	6.52
AL2p-h77	9.39E-08	83	7.14
AL2p-h90	6.12E-08	126	4.35

[0430] In **Table 1**, "N.B." refers to no binding; and "FOB" refers to fold over background.

Example 2: Affinity matured AL2p antibodies show highly improved affinity.

Methods

[0431] Affinity maturation of humanized AL2p variants AL2p-h50 and AL2p-h77 was performed. Briefly, key amino acid residues in the heavy or light chain were selectively mutagenized and mutants that improved binding were selected through additional rounds of screening. This process simultaneously improves specificity, species cross-reactivity, and developability profiles, allowing precise tuning of properties critical for the desired mechanism of action, potency in biological assays, and pre-clinical modeling. Delivery characterizations included Forte Bio and MSD affinity measurements, cell binding and several developability assays. After the first round of affinity maturation, antibodies with elevated affinity also displayed elevated polyspecific reactivity (PSR), which is used to determine unspecific binding of the antibody. Thus, a second round of affinity maturation was performed to improve affinity without elevating PSR.

[0432] The affinity of the affinity matured anti-TREM2 antibodies was determined by measuring their K_D, as well as on- and off-rates by ForteBio OctetRed as previously described by Estep et al., Mabs 2013: 5(2):270-278. Briefly, IgGs were loaded on-line onto AHQ sensors. Sensors were equilibrated off-line in assay buffer for 30 minutes and then monitored on-line for 60 seconds for baseline establishment. For avid binding measurement, sensors with loaded IgGs were exposed to 100 nM antigen (human or cynomolgus monkey TREM2 Fc fusion using the entire TREM2 ECD; only one Fc arm was fused to TREM2) for 3 minutes, afterwards they were transferred to assay buffer for 3 minutes for off-rate measurement. Monovalent binding measurements were obtained by loading human TREM2 Fc fusion antigens to AHQ sensor and followed by exposure to ~100 nM TREM2 antibody Fab. Kinetics data were fit using a 1:1 binding model in the data analysis software provided by ForteBio. Assay was run at room temperature (25°C).

[0433] To examine cell binding of affinity matured anti-TREM2 antibodies, both primary human monocyte derived dendritic cells and recombinant, human TREM2 expressing cells were utilized. For the latter, BW5147.G.1.4 (ATCC® TIB48™) and HEK293T cells stably expressing human TREM2 together with Dap12 using viral infection were established. For primary human monocyte derived dendritic cells, human monocytes were isolated from whole blood using RosetteSep Human monocyte enrichment cocktail (Stemcell technologies) and Ficoll centrifugation per manufacturer protocols. After lysing red blood cells with ACK lysing buffer, monocytes were resuspended in complete media (RPMI, 10% FBS, Pen/Strep, L-glutamine, HEPES, non-essential amino acid, Sodium pyruvate) with 100 ng/ml human GM-CSF (hu-GMCSF) and human IL-4 (hu-IL-4) to differentiate dendritic cells for 6 days.

[0434] Cells were harvested by trypsinization (Hek293T) or scraping (BW and dendritic cells), washed in PBS, counted and plated on 96-well U bottom plates at $1x10^5$ cells/ well. The plates were spun at 1,400rpm for 3 minutes and primary TREM2 or control antibodies were added in FACS buffer

(PBS + 2% FBS) and incubated on ice for one hour. Cells were subsequently centrifuged as before and washed thrice with FACS buffer. Cells were then incubated with anti-human PE conjugated secondary antibody (BD Biosciences) in FACS buffer for 30 minutes on ice. Cells were again washed thrice with FACS buffer and analyzed on a BD FACS Canto or an Intellicyt Flow Cytometer. Binding was measured as mean fluorescence intensity in the APC channel.

Results

[0435] Two rounds of affinity maturation were performed on AL2p variants AL2p-h50 and AL2p-h77. In total, 57 affinity matured clones were selected from the AL2p-h50 lineage and 4 clones from the AL2p-h77 lineage. The heavy chain variable region HVR sequences of the antibodies are depicted in **Tables 2A to 2C**. The light chain variable region HVR sequences of the antibodies are depicted in **Tables 3A to 3C**. The heavy chain framework regions of the antibodies are depicted in **Tables 4A to 4D**. The light chain framework regions of the antibodies are depicted in **Tables 5A to 5D**. The heavy chain variable region sequences of the antibodies are depicted in **Table 6A**. The heavy chain sequences of AL2p variant antibodies are depicted in **Table 6B**. The light chain variable region sequences of the antibodies are depicted in **Table 7A**. The light chain sequences of AL2p variant antibodies are depicted in **Table 7B**.

Table 2A: Heavy chain HVR H1 sequences of anti-TREM2 antibodies

Ab	HVR H1	SEQ ID NO:
AL2p-h50, AL2p-2, AL2p-3, AL2p-4, AL2p-5, AL2p-6, AL2p-33, AL2p-h77, and AL2p-36	YAFSSSWMN	124
AL2p-29, AL2p-30, AL2p-31, AL2p-37, AL2p-58, AL2p-60, AL2p-61, and AL2p-62	YAFSSQWMN	132
AL2p-10, AL2p-11, AL2p-45, AL2p-46, AL2p-47, AL2p-48, and AL2p-49	YAFSSDWMN	136
AL2p-7 and AL2p-8	YAFSLSWMN	157
AL2p-9	YAFSRSWMN	158
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-38, AL2p-39, AL2p-40, AL2p-41, AL2p-42, AL2p-43, AL2p-44, AL2p-50, AL2p-51, AL2p-52, AL2p-53, AL2p-54, AL2p-55, AL2p-56, AL2p-57, and AL2p-59	YAFSSHWMN	159
AL2p-32	YAFSSEWMN	160
AL2p-35	YAFWSSWMN	161
Formula I	$YAFX_1X_2X_3WMN$ X_1 is S or W X_2 is S, L, or R X_3 is S, D, H, Q, or E	121

Table 2B: Heavy chain HVR H2 sequences of anti-TREM2 antibodies

Ab	HVR H2	SEQ ID NO:
AL2p-h50, AL2p-5, AL2p-6, AL2p-9, AL2p-10, AL2p-14, AL2p-15, AL2p-29, AL2p-32,	RIYPGDGDTNYAQKFQG	125

Ab	HVR H2	SEQ ID NO:
AL2p-33, AL2p-h77, and AL2p-35		
AL2p-31 and AL2p-60	RIYPGGGDTNYARKFQG	133
AL2p-37 and AL2p-58	RIYPGGGDTNYAGKFQG	135
AL2p-47, AL2p-48, AL2p-49	RIYPGEGDTNYARKFHG	137
AL2p-45, AL2p-46, and AL2p-61	RIYPGEGDTNYARKFQG	141
AL2p-62	RIYPGEGDTNYAGKFQG	143
AL2p-2 and AL2p-24	RIYPGGGDTNYAQKFQG	162
AL2p-3	RIYPGEGDTNYAQKFQG	163
AL2p-4 and AL2p-27	RIYPGQGDTNYAQKFQG	164
AL2p-7 and AL2p-16	RIYPGDGDTNYAQKFRG	165
AL2p-8, AL2p-11, AL2p-19, AL2p-20, and AL2p-36	RIYPGDGDTNYARKFQG	166
AL2p-12	RIYPGDGDTNYAHKFQG	167
AL2p-13	RIYPGDGDTNYAQKFKG	168
AL2p-17	RIYPGDGDTNYAQKRQG	169
AL2p-18	RIYPGDGDTNYAQKWQG	170
AL2p-21 and AL2p-30	RIYPGDGDTNYAWKFQG	171
AL2p-22	RIYPGDGDTNYAYKFQG	172
AL2p-23	RIYPGDGQTNYAQKRQG	173
AL2p-25, AL2p-38, AL2p-39, and AL2p-40	RIYPGGGDTNYAQKFRG	174
AL2p-26	RIYPGGGDTNYAQKRQG	175
AL2p-28	RIYPGVGDTNYAQKFQG	176
AL2p-41 and AL2p-42	RIYPGEGDTNYAQKFRG	177
AL2p-43 and AL2p-44	RIYPGGGDTNYARKFRG	178
AL2p-50, AL2p-51, AL2p-52, AL2p-53, AL2p-54, AL2p-55, AL2p-56, and AL2p-57	RIYPGEGDTNYAQKFHG	179
AL2p-59	RIYPGEGQTNYAQKRQG	180
Formula II	RIYPGX_1GX_2TNYAX_3K$X_4$$X_5$ G X_1 is D, G, E, Q, or V X_2 is D or Q X_3 is Q, R, H, W, Y, or G X_4 is F, R, or W X_5 is Q, R, K, or H	122

Table 2C: Heavy chain HVR H3 sequences of anti-TREM2 antibodies

Ab	HVR H3	SEQ ID NO:
AL2p-h50, AL2p-2, AL2p-3, AL2p-4, AL2p-5, AL2p-6, AL2p-7, AL2p-10, AL2p-11, AL2p-12, AL2p-13, AL2p-14, AL2p-15, AL2p-17, 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-37, AL2p-50, AL2p-51, AL2p-52, AL2p-53, AL2p-58, AL2p-59, AL2p-60, AL2p-61, and AL2p-62	ARLLRNQPGESYAMDY	126
AL2p-45, AL2p-46, AL2p-47, AL2p-48, AL2p-49, AL2p-54, AL2p-55, AL2p-56, and AL2p-57	ARLLRNKPGESYAMDY	138
AL2p-8 and AL2p-18	ARLLRNQPGSSYAMDY	181
AL2p-9, AL2p-16, AL2p-36, AL2p-38, AL2p-39, AL2p-40, AL2p-41, AL2p-42, AL2p-43, and	ARLLRNQPGASYAMDY	182

Ab	HVR H3	SEQ ID NO:
AL2p-44		
AL2p-35	ARLLRNQPGESYAHDY	183
Formula III	ARLLRNX$_1$PGX$_2$SYAX$_3$D Y X$_1$ is Q or K X$_2$ is E, S, or A X$_3$ is M or H	123

Table 3A: Light chain HVR L1 sequences of anti-TREM2 antibodies

Ab	HVR L1	SEQ ID NO:
AL2p-h50, AL2p-2, AL2p-3, AL2p-4, AL2p-10, AL2p-12, AL2p-31, AL2p-32, AL2p-h77, AL2p-35, AL2p-36, and AL2p-37	RSSQSLVHSNGYTYLH	130
AL2p-45, AL2p-47, AL2p-50, AL2p-52, AL2p-55, and AL2p-56	RTSQSLVHSNAYTYLH	139
AL2p-61 and AL2p-62	RSSQSLVHSNQYTYLH	142
AL2p-5, AL2p-58, and AL2p-60	RSSQSLVHSNRYTYLH	144
AL2p-6	RSSQSLVHSNWYTYLH	184
AL2p-7, AL2p-8, AL2p-13, and AL2p-26	RSSQSLIHSNGYTYLH	185
AL2p-9, AL2p-16, AL2p-18, AL2p-20, AL2p-23, AL2p-25, AL2p-28, and AL2p-33	RTSQSLVHSNGYTYLH	186
AL2p-11, AL2p-14, AL2p-17, AL2p-19, AL2p-22, AL2p-24, AL2p-27, and AL2p-29	RSSRSLVHSNGYTYLH	187
AL2p-15, AL2p-21, and AL2p-30	RSSSSLVHSNGYTYLH	188
AL2p-38 and AL2p-43	RSSRSLVHSNRYTYLH	189
AL2p-39 and AL2p-41	RSSRSLVHSNQYTYLH	190
AL2p-40, AL2p-42, and AL2p-44	RTSRSLVHSNRYTYLH	191
AL2p-46, AL2p-48, AL2p-49, AL2p-51, AL2p-53, AL2p-54, AL2p-57, and AL2p-59	RTSQSLVHSNQYTYLH	192
Formula IV	RX$_1$SX$_2$SLX$_3$HSNX$_4$YTYLH X$_1$ is S or T X$_2$ is Q, R, or S X$_3$ is V or I X$_4$ is G, R, W, Q, or A	127

Table 3B: Light chain HVR L2 sequences of anti-TREM2 antibodies

Ab	HVR L2	SEQ ID NO:
AL2p-h50, AL2p-2, AL2p-3, AL2p-4, AL2p-5, AL2p-6, AL2p-14, AL2p-24, AL2p-29, AL2p-h77, AL2p-35, AL2p-36, AL2p-37, AL2p-58, and AL2p-62	KVSNRFS	131
AL2p-7, AL2p-8, AL2p-10, AL2p-12, AL2p-13, AL2p-22, AL2p-26, AL2p-31, AL2p-32, AL2p-38, AL2p-39, AL2p-40, AL2p-41, AL2p-42, AL2p-43, AL2p-44, AL2p-60, and AL2p-61	KVSNRRS	134
AL2p-9, AL2p-11, AL2p-16, AL2p-17, AL2p-18, AL2p-19, AL2p-20, AL2p-23, AL2p-25, AL2p-27, AL2p-28, AL2p-33, 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, and AL2p-59	KVSNRVS	140
AL2p-15, AL2p-21, and AL2p-30	KVSNRKS	193

Ab	HVR L2	SEQ ID NO:
Formula V	KVSNRX$_1$S X$_1$ is F, R, V, or K	128

Table 3C: Light chain HVR L3 sequences of anti-TREM2 antibodies

Ab	HVR L3	SEQ ID NO:
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, and AL2p-62	SQSTRVPYT	129

Table 4A: Heavy chain framework 1 sequences of anti-TREM2 antibodies

Ab	VH FR1	SEQ ID NO:
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-38, AL2p-39, AL2p-40, AL2p-41, AL2p-42, AL2p-43, AL2p-44, AL2p-45, AL2p-46, AL2p-47, AL2p-48, AL2p-50, AL2p-51, AL2p-54, AL2p-59, AL2p-60, and AL2p-61	QVQLVQSGAEVKKPGSSVKVSCKASG	9
AL2p-33, AL2p-49, AL2p-52, AL2p-53, AL2p-55, AL2p-56, and AL2p-57	EVQLVQSGAEVKKPGSSVKVSCKASG	10
AL2p-h77, AL2p-35, AL2p-36, AL2p-37, AL2p-58, and AL2p-62	QVQLVQSGAEVKKPGASVKVSCKASG	11

Table 4B: Heavy chain framework 2 sequences of anti-TREM2 antibodies

Ab	VH FR2	SEQ ID NO:
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-	WVRQAPGQGLEWMG	12

Ab	VH FR2	SEQ ID NO:
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-59, AL2p-60, and AL2p-61		
AL2p-h77, AL2p-35, AL2p-36, AL2p-37, AL2p-58, and AL2p-62	WVRQAPGQRLEWIG	13

Table 4C: Heavy chain framework 3 sequences of anti-TREM2 antibodies

Ab	VH FR3	SEQ ID NO:
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-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-59, AL2p-60, and AL2p-61	RVTITADESTSTAYMELSSLRSEDTAVYYC	14
AL2p-h77, AL2p-35, AL2p-36, AL2p-37, AL2p-58, and AL2p-62	RVTITADTSASTAYMELSSLRSEDTAVYYC	15

Table 4D: Heavy chain framework 4 sequences of anti-TREM2 antibodies

Ab	VH FR4	SEQ ID NO:
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, and AL2p-62	WGQGTLVTVSS	16

Table 5A: Light chain framework 1 sequences of anti-TREM2 antibodies

Ab	VL FR1	SEQ ID NO:
AL2p-h50, AL2p-2, AL2p-3, AL2p-4, AL2p-5, AL2p-6, AL2p-11, AL2p-17, AL2p-19, AL2p-45, AL2p-46, AL2p-47, AL2p-48, AL2p-49, AL2p-50, AL2p-51, AL2p-52, AL2p-53, AL2p-54, AL2p-55, AL2p-56, and AL2p-57	DVVMTQTPLSLSVTPGQPASISC	17
AL2p-7, AL2p-8, AL2p-9, AL2p-10, AL2p-12, AL2p-13, AL2p-14, AL2p-15, AL2p-16, AL2p-18, 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-38, AL2p-39, AL2p-40, AL2p-41, AL2p-42, AL2p-43, AL2p-44, AL2p-59, AL2p-60, and AL2p-61	GVVMTQTPLSLSVTPGQPASISC	18
AL2p-33	GVVMAQTPLSLSVTPGQPASISC	19
AL2p-h77, AL2p-35, AL2p-36, AL2p-37, AL2p-58, and AL2p-62	DVVMTQSPDSLAVSLGERATINC	20

Table 5B: Light chain framework 2 sequences of anti-TREM2 antibodies

Ab	VL FR2	SEQ ID NO:
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-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-59, AL2p-60, and AL2p-61	WYLQKPGQSPQLLIY	21
AL2p-h77, AL2p-35, AL2p-36, AL2p-37, AL2p-58, and AL2p-62	WYQQKPGQSPKLLIY	22

Table 5C: Light chain framework 3 sequences of anti-TREM2 antibodies

Ab	VL FR3	SEQ ID NO:
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,	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	23

Ab	VL FR3	SEQ ID NO:
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, and AL2p-61		
AL2p-h77, AL2p-35, AL2p-36, AL2p-37, and AL2p-62	GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC	24

Table 5D: Light chain framework 4 sequences of anti-TREM2 antibodies

Ab	VL FR4	SEQ ID NO:
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-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, and AL2p-61	FGQGTKLEIK	25
AL2p-h77, AL2p-35, AL2p-36, AL2p-37, and AL2p-62	FGGGTKVEIK	26

Table 6A: Heavy chain variable region sequences of anti-TREM2 antibodies

Ab	HCVR	SEQ ID NO:
AL2p-h50, AL2p-5, and AL2p-6	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSSWM NWVRQAPGQGLEWMGRIYPGDGDTNYAQKFQGR VTITADESTSTAYMELSSLRSEDTAVYYCARLLRN QPGESYAMDYWGQGTLVTVSS	27
AL2p-2	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSSWM NWVRQAPGQGLEWMGRIYPGGGDTNYAQKFQGR VTITADESTSTAYMELSSLRSEDTAVYYCARLLRN QPGESYAMDYWGQGTLVTVSS	28
AL2p-3	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSSWM NWVRQAPGQGLEWMGRIYPGEGDTNYAQKFQGR VTITADESTSTAYMELSSLRSEDTAVYYCARLLRN	29

Ab	HCVR	SEQ ID NO:
	QPGESYAMDYWGQGTLVTVSS	
AL2p-4	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSSWM NWVRQAPGQGLEWMGRIYPGQGDTNYAQKFQGR VTITADESTSTAYMELSSLRSEDTAVYYCARLLRN QPGESYAMDYWGQGTLVTVSS	30
AL2p-7	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSLSWM NWVRQAPGQGLEWMGRIYPGDGDTNYAQKFRGR VTITADESTSTAYMELSSLRSEDTAVYYCARLLRN QPGESYAMDYWGQGTLVTVSS	31
AL2p-8	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSLSWM NWVRQAPGQGLEWMGRIYPGDGDTNYARKFQGR VTITADESTSTAYMELSSLRSEDTAVYYCARLLRN QPGSSYAMDYWGQGTLVTVSS	32
AL2p-9	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSRSWM NWVRQAPGQGLEWMGRIYPGDGDTNYAQKFQGR VTITADESTSTAYMELSSLRSEDTAVYYCARLLRN QPGASYAMDYWGQGTLVTVSS	33
AL2p-10	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSDW MNWVRQAPGQGLEWMGRIYPGDGDTNYAQKFQ GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGESYAMDYWGQGTLVTVSS	34
AL2p-11	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSDW MNWVRQAPGQGLEWMGRIYPGDGDTNYARKFQ GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGESYAMDYWGQGTLVTVSS	35
AL2p-12	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGDGDTNYAHKFQ GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGESYAMDYWGQGTLVTVSS	36
AL2p-13	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGDGDTNYAQKFK GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGESYAMDYWGQGTLVTVSS	37
AL2p-14 and AL2p-15	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGDGDTNYAQKFQ GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGESYAMDYWGQGTLVTVSS	38
AL2p-16	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGDGDTNYAQKFR GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGASYAMDYWGQGTLVTVSS	39
AL2p-17	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGDGDTNYAQKRQ GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGESYAMDYWGQGTLVTVSS	40
AL2p-18	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGDGDTNYAQKWQ GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGSSYAMDYWGQGTLVTVSS	41
AL2p-19 and AL2p-20	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGDGDTNYARKFQ GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGESYAMDYWGQGTLVTVSS	42

Ab	HCVR	SEQ ID NO:
AL2p-21	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGDGDTNYAWKFQ GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGESYAMDYWGQGTLVTVSS	43
AL2p-22	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGDGDTNYAYKFQ GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGESYAMDYWGQGTLVTVSS	44
AL2p-23	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGDGQTNYAQKRQ GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGESYAMDYWGQGTLVTVSS	45
AL2p-24	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGGGDTNYAQKFQ GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGESYAMDYWGQGTLVTVSS	46
AL2p-25	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGGGDTNYAQKFR GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGESYAMDYWGQGTLVTVSS	47
AL2p-26	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGGGDTNYAQKRQ GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGESYAMDYWGQGTLVTVSS	48
AL2p-27	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGQGDTNYAQKFQ GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGESYAMDYWGQGTLVTVSS	49
AL2p-28	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGVGDTNYAQKFQ GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGESYAMDYWGQGTLVTVSS	50
AL2p-29	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSQW MNWVRQAPGQGLEWMGRIYPGDGDTNYAQKFQ GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGESYAMDYWGQGTLVTVSS	51
AL2p-30	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSQW MNWVRQAPGQGLEWMGRIYPGDGDTNYAWKFQ GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGESYAMDYWGQGTLVTVSS	52
AL2p-31, AL2p-60, and AL2p-h31	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSQW MNWVRQAPGQGLEWMGRIYPGGGDTNYARKFQ GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGESYAMDYWGQGTLVTVSS	53
AL2p-32	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSEWM NWVRQAPGQGLEWMGRIYPGDGDTNYAQKFQGR VTITADESTSTAYMELSSLRSEDTAVYYCARLLRN QPGESYAMDYWGQGTLVTVSS	54
AL2p-33	EVQLVQSGAEVKKPGSSVKVSCKASGYAFSSSWM NWVRQAPGQGLEWMGRIYPGDGDTNYAQKFQGR VTITADESTSTAYMELSSLRSEDTAVYYCARLLRN QPGESYAMDYWGQGTLVTVSS	55
AL2p-h77, AL2p-	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSSW	56

Ab	HCVR	SEQ ID NO:
h26, and AL2p-h90	MNWVRQAPGQRLEWIGRIYPGDGDTNYAQKFQG RVTITADTSASTAYMELSSLRSEDTAVYYCARLLR NQPGESYAMDYWGQGTLVTVSS	
AL2p-35	QVQLVQSGAEVKKPGASVKVSCKASGYAFWSSW MNWVRQAPGQRLEWIGRIYPGDGDTNYAQKFQG RVTITADTSASTAYMELSSLRSEDTAVYYCARLLR NQPGESYAHDYWGQGTLVTVSS	57
AL2p-36	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSSW MNWVRQAPGQRLEWIGRIYPGDGDTNYARKFQG RVTITADTSASTAYMELSSLRSEDTAVYYCARLLR NQPGASYAMDYWGQGTLVTVSS	58
AL2p-37 and AL2p-58	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSQW MNWVRQAPGQRLEWIGRIYPGGGDTNYAGKFQG RVTITADTSASTAYMELSSLRSEDTAVYYCARLLR NQPGESYAMDYWGQGTLVTVSS	59
AL2p-38, AL2p-39, and AL2p-40	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGGGDTNYAQKFR GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGASYAMDYWGQGTLVTVSS	60
AL2p-41 and AL2p-42	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGEGDTNYAQKFRG RVTITADESTSTAYMELSSLRSEDTAVYYCARLLR NQPGASYAMDYWGQGTLVTVSS	61
AL2p-43 and AL2p-44	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGGGDTNYARKFR GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGASYAMDYWGQGTLVTVSS	62
AL2p-45 and AL2p-46	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSDW MNWVRQAPGQGLEWMGRIYPGEGDTNYARKFQG RVTITADESTSTAYMELSSLRSEDTAVYYCARLLR NKPGESYAMDYWGQGTLVTVSS	63
AL2p-47 and AL2p-48	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSDW MNWVRQAPGQGLEWMGRIYPGEGDTNYARKFHG RVTITADESTSTAYMELSSLRSEDTAVYYCARLLR NKPGESYAMDYWGQGTLVTVSS	64
AL2p-49	EVQLVQSGAEVKKPGSSVKVSCKASGYAFSSDWM NWVRQAPGQGLEWMGRIYPGEGDTNYARKFHGR VTITADESTSTAYMELSSLRSEDTAVYYCARLLRN KPGESYAMDYWGQGTLVTVSS	65
AL2p-50 and AL2p-51	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGEGDTNYAQKFH GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGESYAMDYWGQGTLVTVSS	66
AL2p-52 and AL2p-53	EVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHWM NWVRQAPGQGLEWMGRIYPGEGDTNYAQKFHGR VTITADESTSTAYMELSSLRSEDTAVYYCARLLRN QPGESYAMDYWGQGTLVTVSS	67
AL2p-54	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGEGDTNYAQKFH GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNKPGESYAMDYWGQGTLVTVSS	68
AL2p-55, AL2p-56, and AL2p-57	EVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHWM NWVRQAPGQGLEWMGRIYPGEGDTNYAQKFHGR	69

Ab	HCVR	SEQ ID NO:
	VTITADESTSTAYMELSSLRSEDTAVYYCARLLRN KPGESYAMDYWGQGTLVTVSS	
AL2p-61	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSQW MNWVRQAPGQGLEWMGRIYPGEGDTNYARKFQG RVTITADESTSTAYMELSSLRSEDTAVYYCARLLR NQPGESYAMDYWGQGTLVTVSS	70
AL2p-62	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSQW MNWVRQAPGQRLEWIGRIYPGEGDTNYAGKFQG RVTITADTSASTAYMELSSLRSEDTAVYYCARLLR NQPGESYAMDYWGQGTLVTVSS	71
AL2p-h19 and AL2p-h35	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSSWM NWVRQAPGQGLEWMGRIYPGDGDTNYAQKFQGR ATITADTSTSTAYMELSSLRSEDTAVYYCARLLRN QPGESYAMDYWGQGTLVTVSS	72
AL2p-h21	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSSW MNWVRQAPGQGLEWMGRIYPGDGDTNYAQKFQ GRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARL LRNQPGESYAMDYWGQGTLVTVSS	73
AL2p-h22	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSSW MNWVRQAPGQGLEWIGRIYPGDGDTNYAQKFQG RVTMTADTSTSTVYMELSSLRSEDTAVYYCARLL RNQPGESYAMDYWGQGTLVTVSS	74
AL2p-h23	QVQLVQSGAEVKKPGASLKISCKASGYAFSSSWM NWVRQAPGQGLEWIGRIYPGDGDTNYAQKFQGR ATLTADTSTSTAYMELSSLRSEDTAVYYCARLLRN QPGESYAMDYWGQGALVTVSS	75
AL2p-h24	QVQLVQSGAEVVKPGASLKISCKASGYAFSSSWM NWVRQAPGQGLEWIGRIYPGDGDTNYNQKFQGR ATLTADTSTSTAYMELSSLRSEDTAVYFCARLLRN QPGESYAMDYWGQGALVTVSS	76
AL2p-h25	QVQLVQSGAEVKKPGASLKISCKASGYAFSSSWM NWVRQAPGQGLEWIGRIYPGDGDTNYNGEFRVRA TLTADTSTSTAYMELSSLRSEDTAVYYCARLLRNQ PGESYAMDYWGQGALVTVSS	77
AL2p-h27	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSSW MNWVRQAPGQGLEWIGRIYPGDGDTNYNGEFRV RATLTADTSTSTAYMELSSLRSEDTAVYFCARLLR NQPGESYAMDYWGQGTLVTVSS	78
AL2p-h28	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSSW MNWVRQAPGQGLEWIGRIYPGDGDTNYAQKFQG RATLTADTSTSTAYMELSSLRSEDTAVYFCARLLR NQPGESYAMDYWGQGTLVTVSS	79
AL2p-h29	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSSW MNWVRQAPGQGLEWIGRIYPGDGDTNYAQKFQG RATMTADTSTSTAYMELSSLRSEDTAVYYCARLL RNQPGESYAMDYWGQGTLVTVSS	80
AL2p-h30	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSSW MNWVRQAPGQGLEWMGRIYPGDGDTNYAQKFQ GRVTMTADTSTSTAYMELSSLRSEDTAVYYCARL LRNQPGESYAMDYWGQGTLVTVSS	81
AL2p-h32	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSSWM NWVRQAPGQGLEWIGRIYPGDGDTNYNGEFRVRA TLTADTSTTTAYMELSSLRSEDTAVYFCARLLRNQ	82

Ab	HCVR	SEQ ID NO:
	PGESYAMDYWGQGTLVTVSS	
AL2p-h33	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSSWM NWVRQAPGQGLEWIGRIYPGDGDTNYAQKFQGR ATLTADTSTTTAYMELSSLRSEDTAVYFCARLLRN QPGESYAMDYWGQGTLVTVSS	83
AL2p-h34	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSSWM NWVRQAPGQGLEWIGRIYPGDGDTNYAQKFQGR ATITADTSTSTAYMELSSLRSEDTAVYFCARLLRN QPGESYAMDYWGQGTLVTVSS	84
AL2p-h36	EVQLLESGGGLVQPGGSLRLSCAASGYAFSSSWM NWVRQAPGKGLEWIGRIYPGDGDTNYAQKFQGR ATISADTSKNTAYLQMNSLRAEDTAVYYCARLLR NQPGESYAMDYWGQGTLVTVSS	85
AL2p-h42 and AL2p-h59	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSSW MNWVRQAPGQRLEWMGRIYPGDGDTNYAQKFQ GRVTITRDTSASTAYMELSSLRSEDTAVYYCARLL RNQPGESYAMDYWGQGTLVTVSS	86
AL2p-h43	QVQLVQSGAEVKKPGASLKVSCKASGYAFSSSWM NWVRQAPGQRLEWIGRIYPGDGDTNYNGEFRVRA TLTADTSASTAYMELSSLRSEDTAVYFCARLLRNQ PGESYAMDYWGQGTLVTVSS	87
AL2p-h44	QVQLVQSGAEVKKPGASLKVSCKASGYAFSSSWM NWVRQAPGQRLEWIGRIYPGDGDTNYAQKFQGR ATLTADTSASTAYMELSSLRSEDTAVYFCARLLRN QPGESYAMDYWGQGTLVTVSS	88
AL2p-h47	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSSW MNWVRQAPGQGLEWMGRIYPGDGDTNYNGEFRV RVTMTRDTSTSTVYMELSSLRSEDTAVYYCARLLR NQPGESYAMDYWGQGTLVTVSS	89
AL2p-h76	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSSW MNWVRQAPGQRLEWIGRIYPGDGDTNYAQKFQG RATITADTSASTAYMELSSLRSEDTAVYFCARLLR NQPGESYAMDYWGQGTLVTVSS	90
AL2p-59	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGEGQTNYAQKRQ GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGESYAMDYWGQGTLVTVSS	91

Table 6B: Heavy chain sequences of anti-TREM2 antibodies

Ab	HC	SEQ ID NO:
AL2p-58 huIgG1	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSQW MNWVRQAPGQRLEWIGRIYPGGGDTNYAGKFQG RVTITADTSASTAYMELSSLRSEDTAVYYCARLLR NQPGESYAMDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK	198

Ab	HC	SEQ ID NO:
	LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK	
AL2p-58 huIgG1	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSQW MNWVRQAPGQRLEWIGRIYPGGGDTNYAGKFQG RVTITADTSASTAYMELSSLRSEDTAVYYCARLLR NQPGESYAMDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPG	199
AL2p-58 huIgG1 PSEG	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSQW MNWVRQAPGQRLEWIGRIYPGGGDTNYAGKFQG RVTITADTSASTAYMELSSLRSEDTAVYYCARLLR NQPGESYAMDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPASIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHGALHNHYTQKSLS LSPGK	200
AL2p-58 huIgG1 PSEG	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSQW MNWVRQAPGQRLEWIGRIYPGGGDTNYAGKFQG RVTITADTSASTAYMELSSLRSEDTAVYYCARLLR NQPGESYAMDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPASIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHGALHNHYTQKSLS LSPG	201
AL2p-47 huIgG1	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSDW MNWVRQAPGQGLEWMGRIYPGEGDTNYARKFHG RVTITADESTSTAYMELSSLRSEDTAVYYCARLLR NKPGESYAMDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS	202

Ab	HC	SEQ ID NO:
	VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK	
AL2p-47 huIgG1	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSDW MNWVRQAPGQGLEWMGRIYPGEGDTNYARKFHG RVTITADESTSTAYMELSSLRSEDTAVYYCARLLR NKPGESYAMDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPG	203
AL2p-47 huIgG1 PSEG	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSDW MNWVRQAPGQGLEWMGRIYPGEGDTNYARKFHG RVTITADESTSTAYMELSSLRSEDTAVYYCARLLR NKPGESYAMDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPASIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHGALHNHYTQKSLS LSPGK	204
AL2p-47 huIgG1 PSEG	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSDW MNWVRQAPGQGLEWMGRIYPGEGDTNYARKFHG RVTITADESTSTAYMELSSLRSEDTAVYYCARLLR NKPGESYAMDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPASIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHGALHNHYTQKSLS LSPG	205
AL2p-61 huIgG1	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSQW MNWVRQAPGQGLEWMGRIYPGEGDTNYARKFQG RVTITADESTSTAYMELSSLRSEDTAVYYCARLLR NQPGESYAMDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC	206

Ab	HC	SEQ ID NO:
	NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK	
AL2p-61 huIgG1	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSQW MNWVRQAPGQGLEWMGRIYPGEGDTNYARKFQG RVTITADESTSTAYMELSSLRSEDTAVYYCARLLR NQPGESYAMDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPG	207
AL2p-40 huIgG1	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGGGDTNYAQKFR GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGASYAMDYWGQGTLVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPGK	208
AL2p-40 huIgG1	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGGGDTNYAQKFR GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGASYAMDYWGQGTLVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPG	209
AL2p-44 huIgG1	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGGGDTNYARKFR GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL	210

Ab	HC	SEQ ID NO:
	RNQPGASYAMDYWGQGTLVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPGK	
AL2p-44 huIgG1	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGGGDTNYARKFR GRVTITADESTSTAYMELSSLRSEDTAVYYCARLL RNQPGASYAMDYWGQGTLVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPG	211
AL2p-41 huIgG1	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGEGDTNYAQKFRG RVTITADESTSTAYMELSSLRSEDTAVYYCARLLR NQPGASYAMDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK	212
AL2p-41 huIgG1	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSHW MNWVRQAPGQGLEWMGRIYPGEGDTNYAQKFRG RVTITADESTSTAYMELSSLRSEDTAVYYCARLLR NQPGASYAMDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPG	213

Table 7A: Light chain variable region sequences of anti-TREM2 antibodies

Ab	LCVR	SEQ ID NO:
AL2p-h50, AL2p-2, AL2p-3, AL2p-4, AL2p-h42, AL2p-h43, AL2p-h44, and AL2p-h47	DVVMTQTPLSLSVTPGQPASISCRSSQSLVHSNGYTY LHWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQGTKL EIK	92
AL2p-5	DVVMTQTPLSLSVTPGQPASISCRSSQSLVHSNRYTY LHWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQGTKL EIK	93
AL2p-6	DVVMTQTPLSLSVTPGQPASISCRSSQSLVHSNWYT YLHWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGS GTDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQGTK LEIK	94
AL2p-7, AL2p-8, AL2p-13, and AL2p-26	GVVMTQTPLSLSVTPGQPASISCRSSQSLIHSNGYTY LHWYLQKPGQSPQLLIYKVSNRRSGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQGTKL EIK	95
AL2p-9, AL2p-16, AL2p-18, AL2p-20, AL2p-23, AL2p-25, and AL2p-28	GVVMTQTPLSLSVTPGQPASISCRTSQSLVHSNGYTY LHWYLQKPGQSPQLLIYKVSNRVSGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQGTKL EIK	96
AL2p-10, AL2p-12, AL2p-31, and AL2p-32	GVVMTQTPLSLSVTPGQPASISCRSSQSLVHSNGYTY LHWYLQKPGQSPQLLIYKVSNRRSGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQGTKL EIK	97
AL2p-11, AL2p-17, and AL2p-19	DVVMTQTPLSLSVTPGQPASISCRSSRSLVHSNGYTY LHWYLQKPGQSPQLLIYKVSNRVSGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQGTKL EIK	98
AL2p-14, AL2p-24, and AL2p-29	GVVMTQTPLSLSVTPGQPASISCRSSRSLVHSNGYTY LHWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQGTKL EIK	99
AL2p-15, AL2p-21, and AL2p-30	GVVMTQTPLSLSVTPGQPASISCRSSSSLVHSNGYTY LHWYLQKPGQSPQLLIYKVSNRKSGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQGTKL EIK	100
AL2p-22	GVVMTQTPLSLSVTPGQPASISCRSSRSLVHSNGYTY LHWYLQKPGQSPQLLIYKVSNRRSGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQGTKL EIK	101
AL2p-27	GVVMTQTPLSLSVTPGQPASISCRSSRSLVHSNGYTY LHWYLQKPGQSPQLLIYKVSNRVSGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQGTKL EIK	102
AL2p-33	GVVMAQTPLSLSVTPGQPASISCRTSQSLVHSNGYTY LHWYLQKPGQSPQLLIYKVSNRVSGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQGTKL EIK	103

Ab	LCVR	SEQ ID NO:
AL2p-h77, AL2p-35, AL2p-36, AL2p-37, and AL2p-h76	DVVMTQSPDSLAVSLGERATINCRSSQSLVHSNGYT YLHWYQQKPGQSPKLLIYKVSNRFSGVPDRFSGSGS GTDFTLTISSLQAEDVAVYYCSQSTRVPYTFGGGTK VEIK	104
AL2p-38 and AL2p-43	GVVMTQTPLSLSVTPGQPASISCRSSRSLVHSNRYTY LHWYLQKPGQSPQLLIYKVSNRRSGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQGTKL EIK	105
AL2p-39 and AL2p-41	GVVMTQTPLSLSVTPGQPASISCRSSRSLVHSNQYTY LHWYLQKPGQSPQLLIYKVSNRRSGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQGTKL EIK	106
AL2p-40, AL2p-42, and AL2p-44	GVVMTQTPLSLSVTPGQPASISCRTSRSLVHSNRYTY LHWYLQKPGQSPQLLIYKVSNRRSGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQGTKL EIK	107
AL2p-45, AL2p-47, AL2p-50, AL2p-52, AL2p-55, and AL2p-56	DVVMTQTPLSLSVTPGQPASISCRTSQSLVHSNAYTY LHWYLQKPGQSPQLLIYKVSNRVSGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQGTKL EIK	108
AL2p-46, AL2p-48, AL2p-49, AL2p-51, AL2p-53, AL2p-54, and AL2p-57	DVVMTQTPLSLSVTPGQPASISCRTSQSLVHSNQYTY LHWYLQKPGQSPQLLIYKVSNRVSGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQGTKL EIK	109
AL2p-61	GVVMTQTPLSLSVTPGQPASISCRSSQSLVHSNQYTY LHWYLQKPGQSPQLLIYKVSNRRSGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQGTKL EIK	110
AL2p-62	DVVMTQSPDSLAVSLGERATINCRSSQSLVHSNQYT YLHWYQQKPGQSPKLLIYKVSNRFSGVPDRFSGSGS GTDFTLTISSLQAEDVAVYYCSQSTRVPYTFGGGTK VEIK	111
AL2p-58	DVVMTQSPDSLAVSLGERATINCRSSQSLVHSNRYT YLHWYQQKPGQSPKLLIYKVSNRFSGVPDRFSGSGS GTDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQGTK LEIK	112
AL2p-60	GVVMTQTPLSLSVTPGQPASISCRSSQSLVHSNRYTY LHWYLQKPGQSPQLLIYKVSNRRSGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQGTKL EIK	113
AL2p-h19	DIVMTQTPLSLSVTPGQPASISCRSSQSLVHSNGYTY LHWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQGTKL EIK	114
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-	DVVMTQTPLSLSVTPGQPASISCRSSQSLVHSNGYTY LHWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSG TDFTLKISRVEAEDLGVYFCSQSTRVPYTFGQGTKLE IK	115

Ab	LCVR	SEQ ID NO:
h34, AL2p-h35, AL2p-h36		
AL2p-h59	DIVMTQSPLSLPVTPGEPASISCRSSQSLVHSNGYTYL HWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSGSGT DFTLKISRVEAEDVGVYYCSQSTRVPYTFGGGTKVEI K	116
AL2p-h90	DVQMTQSPSSLSASVGDRVTITCRSSQSLVHSNGYT YLHWYQQKPGKSPKLLIYKVSNRFSGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCSQSTRVPYTFGGGTKV EIK	117
AL2p-59	GVVMTQTPLSLSVTPGQPASISCRTSQSLVHSNQYTY LHWYLQKPGQSPQLLIYKVSNRVSGVPDRFSGSGSG TDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQGTKL EIK	118

Table 7B: Light chain sequences of anti-TREM2 antibodies

Ab	LC	SEQ ID NO:
AL2p-58 huIgG1, and AL2p-58 huIgG1 PSEG	DVVMTQSPDSLAVSLGERATINCRSSQSLVHSNRY TYLHWYQQKPGQSPKLLIYKVSNRFSGVPDRFSGS GSGTDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQ GTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC	214
AL2p-47 huIgG1, and AL2p-47 huIgG1 PSEG	DVVMTQTPLSLSVTPGQPASISCRTSQSLVHSNAYT YLHWYLQKPGQSPQLLIYKVSNRVSGVPDRFSGSG SGTDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQG TKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC	215
AL2p-61 huIgG1	GVVMTQTPLSLSVTPGQPASISCRSSQSLVHSNQYT YLHWYLQKPGQSPQLLIYKVSNRRSGVPDRFSGSG SGTDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQG TKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC	216
AL2p-41 huIgG1	GVVMTQTPLSLSVTPGQPASISCRSSRSLVHSNQYT YLHWYLQKPGQSPQLLIYKVSNRRSGVPDRFSGSG SGTDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQG TKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC	217
AL2p-40 huIgG1, and AL2p-44 huIgG1	GVVMTQTPLSLSVTPGQPASISCRTSRSLVHSNRYT YLHWYLQKPGQSPQLLIYKVSNRRSGVPDRFSGSG SGTDFTLKISRVEAEDVGVYYCSQSTRVPYTFGQG TKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC	218

[0436] Clones were tested for affinity using OctetRed and a strong increase in monovalent affinity was observed (**Table 8**). In addition, clones were tested for binding to cynomolgus monkey TREM2 and all clones were able to bind monovalently (**Table 8**). Clones were tested for binding to human TREM2-expressing BW cells and improved affinity was observed in this setting as well (**Table 8**). In addition, antibodies showed increased binding to primary human dendritic cells that express human TREM2 endogenously (**Table 8**).

[0437] The parental AL2p antibody contains two residues that are subject to de-amidation, a DG in VH-CDR2 and a NG in VL-CDR1. When testing affinity matured AL2p variant antibodies, five clones with amino acid substitutions at these positions were produced: AL2p-2 (DG to GG), AL2p-3 (DG to EG), AL2p-4 (DG to QG), AL2p-5 (NG to NR), AL2p-6 (NG to NW). These variants were confirmed to retain that same affinity as the parental AL2p-h50 antibody (**Table 8**). Additionally, variants AL2p-38 to AL2p-57 already included amino acid substitutions at these positions, which are DG to GG or EG in VH-CDR2 together with NG to NR or NQ or NA in VL-CDR1. These clones show improved affinity and function compared to the parental clone, suggesting that the combination of amino acid substitutions at these positions does not affect function.

Table 8: Summary of binding experiments of AL2p variant antibodies

Antibody	ForteBio Fab K_D huTREM2-Fc (M) monovalent	ForteBio IgG K_D huTREM2-Fc (M) avid	ForteBio Fab K_D cyno TREM2-Fc (M) monovalent	cell binding huT2 BW K_D (nM)	MFI binding to huDCs
AL2p-h50	1.12E-07	1.19E-09	7.70E-06	3.7	26
AL2p-h77	1.02E-07	1.17E-09	1.84E-07	3.9	162
AL2p-2	6.33E-08	8.37E-10	1.40E-06	2.2	
AL2p-3	1.00E-07	1.19E-09	4.58E-06	2.3	
AL2p-4	1.32E-07	8.17E-10	P.F.	2.1	
AL2p-5	9.92E-08	1.00E-09	4.63E-06	2.0	
AL2p-6	2.59E-07	1.06E-09	1.15E-06	4.2	
AL2p-7	8.38E-09	4.27E-10	8.95E-09	1.6	
AL2p-8	4.01E-09	3.00E-10	3.10E-09	1.2	310
AL2p-9	6.44E-09	3.49E-10	5.63E-09	1.1	322
AL2p-10	1.85E-08	8.35E-10	2.77E-08	3.1	
AL2p-11	9.83E-09	5.36E-10	1.02E-08	2.4	
AL2p-12	5.86E-09	5.14E-10	5.25E-09	1.8	
AL2p-13	4.80E-09	3.40E-10	4.93E-09	1.5	
AL2p-14	4.74E-09	3.15E-10	4.66E-09	2.1	
AL2p-15	8.85E-09	5.38E-10	8.76E-09	2.2	262
AL2p-16	1.83E-09	2.22E-10	1.36E-09	1.2	327
AL2p-17	4.83E-09	2.55E-10	4.62E-09	1.4	
AL2p-18	3.17E-09	2.29E-10	2.73E-09	1.3	
AL2p-19	4.02E-09	3.03E-10	4.01E-09	1.4	
AL2p-20	4.73E-09	3.50E-10	4.72E-09	1.2	
AL2p-21	4.15E-09	3.99E-10	3.84E-09	1.5	
AL2p-22	1.58E-09	2.19E-10	1.28E-09	1.5	
AL2p-23	4.35E-09	3.34E-10	4.16E-09	1.2	

Antibody	ForteBio Fab K_D huTREM2-Fc (M) monovalent	ForteBio IgG K_D huTREM2-Fc (M) avid	ForteBio Fab K_D cyno TREM2-Fc (M) monovalent	cell binding huT2 BW K_D (nM)	MFI binding to huDCs
AL2p-24	2.10E-09	2.33E-10	1.63E-09	1.7	
AL2p-25	2.34E-09	2.20E-10	1.76E-09	1.7	
AL2p-26	3.15E-09	2.01E-10	2.69E-09	1.1	296
AL2p-27	1.99E-09	2.74E-10	1.82E-09	1.5	
AL2p-28	7.60E-09	4.17E-10	7.91E-09	2.2	
AL2p-29	6.38E-09	4.03E-10	6.47E-09	1.3	
AL2p-30	6.50E-09	3.77E-10	5.66E-09	1.2	
AL2p-31	4.03E-09	3.17E-10	3.44E-09	1.0	288
AL2p-32	3.60E-08	1.12E-09	3.48E-08	2.8	
AL2p-33	1.03E-08	8.89E-10	8.84E-10	4.5	
AL2p-35	2.84E-08	1.85E-09	2.46E-08	3.6	130
AL2p-36	1.21E-08	4.95E-10	7.38E-09	1.7	240
AL2p-37	2.38E-08	7.79E-10	1.61E-08	2.9	194
AL2p-38	6.23E-10		3.70E-10	4.79	499
AL2p-39	6.31E-10		3.46E-10	1.53	590
AL2p-40	6.02E-10		3.70E-10	2.27	547
AL2p-41	7.24E-10		3.52E-10	1.31	534
AL2p-42	8.29E-10		3.12E-10	1.91	662
AL2p-43	4.93E-10		3.60E-10	5.01	1035
AL2p-44	4.10E-10		2.71E-10	4.18	1467
AL2p-45	1.78E-08		2.09E-08	1.54	318
AL2p-46	1.30E-08		1.61E-08	1.33	187
AL2p-47	1.48E-08		1.63E-08	1.09	372
AL2p-48	1.12E-08		1.49E-08	1.40	408
AL2p-49	1.16E-08		1.41E-08	1.15	413
AL2p-50	2.39E-08		3.61E-08	1.80	235
AL2p-51	2.12E-08		2.72E-08	1.92	195
AL2p-52	2.70E-08		2.80E-08	2.42	224
AL2p-53	2.11E-08		3.13E-08	1.72	159
AL2p-54	1.39E-08		1.68E-08	2.30	235
AL2p-55	1.85E-08		2.26E-08	2.05	141
AL2p-56	1.87E-08		1.88E-08	2.01	155
AL2p-57	1.78E-08		1.76E-08	1.83	152
AL2p-59	3.85E-09		3.95E-09		
AL2p-61	3.73E-06		3.84E-09		
AL2p-62	2.11E-08		1.94E-08		
AL2p-58	1.33E-08		1.24E-08	0.51	

[0438] In **Table 8**, experiments for clones AL2p-2 to AL2p-37 were performed separately from experiments characterizing AL2p-38 to AL2p-57. Binding to human dendritic cells (DC's) was performed on different donors for these two sets of antibodies and because there is a large donor to donor variability in TREM2 expression, MFI values cannot be directly compared across donors. P.F.= poor fit; MFI= mean fluorescence intensity.

Example 3: Affinity matured AL2p antibodies show highly improved function.

Methods

[0439] The ability of plate-bound, full-length anti-TREM2 antibodies to activate human TREM2-dependent genes was evaluated using a luciferase reporter gene under the control of an NFAT (nuclear factor of activated T-cells) promoter. The cell line BW5147.G.1.4, derived from mouse thymus lymphoma T lymphocytes, was infected with a human TREM2/DAP12 fusion protein, and with Cignal Lenti NFAT-Luciferase virus (Qiagen). To test the antibodies, plate bound, anti-TREM2 and isotype control antibodies were dissolved in PBS, plated on tissue culture plates at a concentration of 10 µg/ml and incubated overnight at 4°C to allow the antibodies to absorb to the plate. After washing of the plates, cells were plated on the plate-bound antibodies and incubated for 4 to 6 hours at 37°C. To test antibodies in solution, they were added to the culture plates together with the cells and incubated for 4 to 6 hours at 37°C. Luciferase activity was measured by adding OneGlo Reagent (Promega) to each well and incubating for 3 minutes at room temperature on a plate shaker. Luciferase signal was measured using a BioTek plate reader.

[0440] The ability of soluble, full-length anti-TREM2 antibodies to change the activity of natural ligands of human TREM2 was evaluated using a luciferase reporter gene assay as well. Cells were incubated for 4 to 6 hours, together with soluble anti-TREM2 and isotype control antibodies, on plates that were pre-coated with phosphatidylserine (lipid was dissolved and titrated in methanol, added to the plates and methanol was allowed to evaporate overnight). Cells were lysed and luciferase activity was measured by adding OneGlo Reagent (Promega) to each well and incubating for 3 minutes at room temperature on a plate shaker. Luciferase signal was measured using a BioTek plate reader.

[0441] To assess viability of human dendritic cells and macrophages human monocytes were isolated from whole blood using RosetteSep Human monocyte enrichment cocktail (Stemcell technologies) and Ficoll centrifugation per manufacturer protocols. After lysing red blood cells with ACK lysing buffer, monocytes were resuspended in complete media (RPMI, 10% FBS, Pen/Strep, L-glutamine, HEPES, non-essential amino acid, Sodium pyruvate) with 100 ng/ml human GM-CSF (hu-GMCSF) and human IL-4 (hu-IL-4) to differentiate dendritic cells for 6 days. Macrophages were differentiated for 5-6 days in complete media (RPMI, 10% FBS, Pen/Strep, L-glutamine, HEPES, non-essential amino acid, Sodium pyruvate) with 100 ng/ml human hu-MCSF.

[0442] Anti-TREM2 antibodies or control antibody were added into a 96 well plate and left at 4°C overnight. The next day, the plate was washed twice with PBS. Cells were plated at 25000 cells/well and cultured for 2 days. Cells were then quantified using the CellTiter-Glo Luminescent cell viability kit (Promega) per manufacturer's protocol and luminescence was determined as a measure of cell viability.

Results

[0443] To test whether increased affinity correlates with enhanced function, affinity matured anti-TREM2 antibodies were tested first for their ability to trigger TREM2 signaling when added either soluble or plate bound to BW cells expressing human TREM2/Dap12 and the NFAT:luciferase reporter. The parental AL2p antibody can cluster and activate TREM2 signaling when added in a soluble solution to the cells or when bound to the plate. In line with their increase in affinity, AL2p affinity matured variant antibodies displayed enhanced ability to cluster and activate TREM2, both in the plate bound and soluble format (**Table 9A**). Particularly in the plate bound format, affinity matured antibodies strongly enhanced NFAT:luciferase signaling compared to the parental humanized clones (**Table 9A**).

[0444] **FIG. 3A** and **FIG. 3B** show the results of functional analysis of AL2p affinity matured antibodies AL2p-58, AL2p-59, AL2p-60, AL2p-62, AL2p-47, and isotype control IgG antibody. As in **Table 10A**, antibodies were tested for their ability to induce TREM2 signaling in BW cells expressing NFAT:luciferase, added either soluble or plate bound. Antibody AL2p-58 is an affinity matured antibody derived from the AL2p-62 clone, but that includes light chain framework regions from two different germlines (i.e., parental humanized anti-TREM2 antibody clones). In particular, the AL2p-58 antibody has the light chain framework regions 1 and 2 (FR1 and FR2) from the AL2p-h77 germline and has the light chain framework regions 3 and 4 (FR3 and FR4) from the AL2p-h50 germline. In contrast, all four light chain framework regions of antibody AL2p-62 are from the AL2p-h77 germline. The results show that antibody AL2p-58 has surprisingly good TREM2 signaling-inducing activity, particularly as compared to the AL2p-62 antibody, despite both antibodies sharing the same variable CDR's, except for CDR-H2 and CDR-L1 (**FIG. 3A** and **FIG. 3B**). However, the differences with the CDR-H2 and CDR-L1 sequences of AL2p-58 and AL2p-62 are due to different hotfixes, which were not shown to positively or negatively affect antibody affinity or function (**Table 9A**). The results also indicate that while AL2p-58 has the sane heavy chain variable region sequence as AL2p-37, AL2p-58 shows an unexpectedly high improvement in functional properties compared to AL2-p37.

[0445] The results in **Table 10A** also indicate that AL2p-47 shows surprisingly better functional properties, as well as higher affinity to cell-expressed TREM2, as compared to antibodies AL2p-45, AL2p-55, and AL2p-56, which all share the same light chain variable domain and very similar heavy chain variable domain sequences. In particular, the only difference in sequence between AL2p-47 and AL2p-45 is in the HVR-H2, where AL2p-47 has an H at the 16^{th} position and AL2p-45 has a Q (**Table 2B**). The differences in sequence between AL2-47 and AL2p-55 and AL2p-56 are a single amino acid difference in HVR-H1 (**Table 2A**), a single amino acid difference in heavy chain FR1 (**Table 4A**), and a single amino acid difference in HVR-H2, where AL2p-47 has an R at the 13^{th} position and both AL2p-55 and AL2p-56 have a Q (**Table 2B**). Based on these results, it appears that the combination of the R at the 13^{th} position of the HVR-H2 sequence and the H at the 16^{th} position of

HVR-H2 sequence of antibody AL2p-47 shows a surprising effect compared to the R at the 13th position alone (as is the case for AL2-p45) or the H at the 16th position alone (as is the case for AL2p-55 and AL2p-56), especially given that AL2p-47 has similar affinity to human TREM2 protein as do AL2p-45, AL2p-55, and AL2p-56.

[0446] **FIG. 3C** shows the ability of plate bound affinity matured antibody variants to induce TREM2 signaling as measured by the NFAT:luciferase reporter assay. The results indicate a dramatic (up to 4-fold) increase in efficacy of affinity matured antibodies as compared to the corresponding parental humanized AL2p antibody (h50 or h77) or the parental murine IgG1 antibody (AL2p).

[0447] TREM2 was shown to affect survival of primary murine macrophages and microglia *in vitro*, with TREM2 knock-out cells showing reduced viability (Wang et al., Cell 2015, 160(6):1061-1071). To verify functionality of AL2p variant antibodies in primary cells, human monocyte derived macrophages or dendritic cells were stimulated with plate bound AL2p variant antibodies and the viability of cells was measured 2 days later. It was found that plate bound AL2p parental antibody increases viability in a dose dependent fashion. Compared to the parental clone, affinity matured AL2p variant antibodies increase viability even further (**Tables 9A and 10A**).

[0448] Clones AL2p-23, AL2p-31 and AL2p-37 were produced in CHO cells containing the following variants: DG to EG and NG to NQ. These clones retain the affinity of the parental clones (**Table 9B**).

Table 9A: Functional analysis affinity matured antibodies

Antibody	Luciferase activation soluble 10nM IgG, FOC	Luciferase activation plate bound 33nM IgG, FOC	Survival huDCs plate bound IgG, AUC
AL2p-h50	1.26	6.83	337353
AL2p-h77	1.47	6.77	380527
AL2p-2	1.70	7.36	461171
AL2p-3	1.29	6.03	363252
AL2p-4	1.45	7.42	495712
AL2p-5	1.27	9.99	709979
AL2p-6	1.20	5.39	546995
AL2p-7	2.35	18.87	n.d.
AL2p-8	2.78	n.d.	1088000
AL2p-9	2.62	15.21	976481
AL2p-10	1.60	4.63	n.d.
AL2p-11	1.71	23.64	n.d.
AL2p-12	1.96	15.80	n.d.
AL2p-13	2.17	16.53	n.d.
AL2p-14	1.79	22.07	n.d.
AL2p-15	1.80	7.54	487849

Antibody	Luciferase activation soluble 10nM IgG, FOC	Luciferase activation plate bound 33nM IgG, FOC	Survival huDCs plate bound IgG, AUC
AL2p-16	2.60	16.87	880480
AL2p-17	2.13	23.83	n.d.
AL2p-18	2.06	8.46	n.d.
AL2p-19	2.06	25.85	n.d.
AL2p-20	2.12	22.45	n.d.
AL2p-21	1.83	13.05	n.d.
AL2p-22	1.75	24.86	n.d.
AL2p-23	2.53	29.75	1108000
AL2p-24	2.12	24.13	n.d.
AL2p-25	2.35	22.28	n.d.
AL2p-26	2.59	25.91	1113000
AL2p-27	2.06	24.39	n.d.
AL2p-28	2.14	9.27	n.d.
AL2p-29	2.17	26.64	1113000
AL2p-30	2.31	15.78	n.d.
AL2p-31	2.83	28.25	1209000
AL2p-32	1.47	4.90	n.d.
AL2p-33	1.72	3.21	n.d.
AL2p-35	2.05	5.15	453094
AL2p-36	2.64	22.70	1143000
AL2p-37	2.16	9.42	679678

[0449] **Table 9A** shows a functional analysis of a set of AL2p affinity matured antibodies, as compared to the parental antibodies AL2p-h50 and AL2p-h77. In the Table, n.d.= not determined; AUC= area under curve; FOC= fold over control, where the control is an isotype control antibody. Clones AL2p-2 to AL2p-6 are variants of parental antibody AL2p-h50 that include hotfixes to eliminate a de-amidation site.

Table 9B: **Testing HVR variants for anti-TREM2 antibodies**

Antibody	VH-HVR2 variants	VL-HVR1 variants	cell binding huT2 BW K_D (M)	luciferase activation, soluble IgG, EC_{50} (M)
AL2p-h50	none	none	3.7E-01	6.31E-08
AL2p-h77	none	none	3.90E-01	2.01E-08
AL2p-2	DG to GG	none	2.2E-01	2.30E-08
AL2p-3	DG to EG	none	2.3E-09	5.00E-08
AL2p-4	DG to QG	none	2.1E-09	6.62E-08
AL2p-5	none	NG to NR	2.0E-09	3.81E-08
AL2p-6	none	NG to NW	4.2E-09	3.86E-08

Antibody	VH-HVR2 variants	VL-HVR1 variants	cell binding huT2 BW K_D (M)	luciferase activation, soluble IgG, EC_{50} (M)
AL2p-59	DG to EG	NG to NQ	1.24E-09	1.12E-08
AL2p-60	GG to EG	NG to NQ	1.12E-09	1.03E-08
AL2p-62	DG to EG	NG to NQ	2.63E-09	2.51E-08
AL2p-31	DG to GG	none	1.23E-09	6.92E-09

[0450] In **Table 9B**, values in grey boxes were obtained in a different experiment than the other values of the same column.

Table 10A: Functional analysis of AL2p affinity matured antibodies that include amino acid substitutions at positions susceptible to de-amidation

Antibody	BW Luc assay plate bound 7.3nM IgG, FOC	BW Luc assay soluble 7.3nM IgG, FOC	DC viability (AUC)	Mac viability (AUC)
AL2p-31	7.49	4.48	860213	83712
AL2p-38	4.47	4.98	785505	39036
AL2p-39	8.12	3.81	850801	66855
AL2p-40	8.49	9.92	824725	63235
AL2p-41	7.61	2.92	859989	80670
AL2p-42	6.52	5.95	780879	57916
AL2p-43	5.41	8.84	n.d.	n.d.
AL2p-44	7.17	11.50	750071	74651
AL2p-45	2.29	2.38	543378	3676
AL2p-46	1.64	2.98	596898	6044
AL2p-47	3.54	3.48	771393	22055
AL2p-48	3.25	3.65	769717	23589
AL2p-49	3.12	3.28	753554	15109
AL2p-50	1.19	2.07	286306	-10420
AL2p-51	1.22	2.30	259485	-11153
AL2p-52	1.30	1.75	283169	-13548
AL2p-53	1.45	2.32	234316	-10245
AL2p-54	1.53	2.17	569761	-7639
AL2p-55	1.49	2.08	630883	-5284
AL2p-56	1.51	2.02	643293	-7621
AL2p-57	1.41	2.03	505964	-3564

[0451] **Table 10A** shows a functional analysis of AL2p affinity matured antibodies from the second round of affinity maturation. Antibodies were tested for their ability to induce TREM2 signaling in BW cells expressing NFAT:luciferase, added either soluble or plate bound, as well as their ability to increase viability of macrophages or dendritic cells in a plate bound format. In **Table**

10A, n.d.= not determined; AUC= area under curve. DC= primary human dendritic cells; Mac= primary human macrophages; FOC= fold over control.

Table 10B: Functional analysis of AL2p affinity matured antibody variants

Antibody	luciferase activation, soluble IgG, EC_{50} (nM)	luciferase activation, plate bound IgG, EC_{50} (nM)
AL2p	19.3	n.d.
AL2p-31	1.14	10.1
AL2p-47	104	206
AL2p-58	14	36

[0452] **Table 10B** and **FIG. 4A** and **FIG. 4B** show the results of functional analysis of parental mouse antibody AL2p, affinity matured antibodies AL2p-31, AL2p-47, AL2p-58, and a control antibody. For antibodies AL2p-31 and AL2p-58, the antibodies were generated using both a human IgG constant region (huFC) or a mouse IgG constant region (msFc). Antibodies were tested for their ability to induce TREM2 signaling in BW cells expressing NFAT:luciferase, added either soluble or plate bound, as well as their ability to increase viability of macrophages or dendritic cells in a plate bound format. In **Table 10B**, n.d.= not determined. The results indicate that the affinity matured antibodies had better TREM2 signaling-inducing activity and lower EC_{50} than the parental mouse antibody AL2p (**Table 10B** and **FIG. 4A** and **FIG. 4B**).

[0453] **Table 10C** shows a comparison of antibody characteristics between affinity matured antibodies AL2p-31, AL2p-47, and AL2p-58, and the parental mouse antibody AL2p.

Table 10C: Comparison of affinity matured antibodies to parental murine antibody

Characteristic	AL2p	AL2p-47	AL2p-31	AL2p-58
Germline	Murine	VH1-69; CK2D-29	VH1-69; CK2D-29	VH1-69; VK4-1/VK2D-29
Fab K_D (nM) to recombinant hTREM2	1.12×10^{-7}	1.27×10^{-8}	3.73×10^{-9}	1.33×10^{-8}
Fab k_{on} (M) to recombinant hTREM2	1.94×10^{5}	2.67×10^{5}	3.35×10^{5}	3.26×10^{5}
Fab k_{off} (M) to recombinant hTREM2	3.4×10^{-3}	3.40×10^{-3}	1.26×10^{-3}	4.33×10^{-3}
Binding to hTREM2 expressing cell line K_D (nM)	3.04	1.22	0.56	0.51
Reporter assay plate bound IgG (EC_{50}, nM)	Low	206.3	10.1	36.1
Reporter assay soluble IgG (EC_{50}, nM)	19	104.7	11.4	14.0
Dendritic cell viability	- (1)	+ (2)	++ (3)	++ (3)

Example 4: PK/PD analysis of affinity matured AL2p antibodies

Methods

[0454] Human TREM2 transgenic (Tg) mice as well as wild-type (WT) littermate controls that only express murine TREM2 were used in a PK/PD study to test both the half-life of different AL2p affinity matured variant antibodies in the presence or absence of target engagement, as well as the effect of AL2p antibody on soluble TREM2 in the plasma of TREM2 Tg mice.

[0455] Human TREM2 Tg mice were injected intraperitoneally on day 0 with 15 mg/kg of HEK or CHO produced AL2p variants AL2p-31-HF as WT and PSEG huIgG1, AL2p-23-HF, AL2p-37-HF, AL2p-58-HF, AL2p-40, AL2p-41, AL2p-47, all in a huIgG1 backbone, as well as control huIgG1 (n=2-3 mice/group). Human TREM2 Tg mice were injected intraperitoneally on day 0 with 15 mg/kg of HEK or CHO produced AL2p variants AL2p-60 as PSEG huIgG1, AL2p-47 as huIgG1, AL2p-58 as huIgG1, as well as control huIgG1 (n=2-3 mice/group). Blood was collected by tail vein puncture at the following time points: 4h after injection, days 1, 3, 6, 10 and 14. For plasma isolation, the blood was collected in heparinized tubes and centrifuged at 10,000xg for 10 min at 4°C. Plasma supernatant was collected at stored at -80°C.

[0456] Levels of human IgG1 antibodies in the plasma were determined using a custom (MesoScale Discovery) MSD assay. Briefly, 96-well multi-array plates (MesoScale Discovery) were coated overnight at 4°C with 50µl of 1µg/ml of goat anti-human Fab fragment specific for IgG (Jackson Immuno Research) at 500rpm on a plate shaker. Plates were washed three times in 150µl wash buffer (PBS + 0.05% Tween) and blocked in binding buffer (PBS + 1% BSA) for 1 hr at RT at 500rpm on a plate shaker. Plasma was diluted in binding buffer at 1:200 and 1:10,000 and added to the blocked plates and incubated for 1 h at 37°C. Control huIgG1 was used as a standard. Plates were subsequently washed three times in 150µl wash buffer and incubated with a goat anti-human sulfo-tag conjugated secondary antibody (MesoScale Discovery) at 1µg/ml in binding buffer for 1 hr at RT. Plates were subsequently washed three times in 150µl wash buffer and 150µl 1x Read Buffer was added to each well and the plates were imaged in a Sector Imager (MesoScale Discovery). Data were analyzed using GraphPad Prism.

[0457] For the human specific TREM2 ELISA, capture antibody T2KO8F11 was plated at 2 µg/ml in PBS overnight at 4C (100 µL per well in high bind Elisa plates). The plates were washed thrice with a plate washer and 300 µL PBS + 0.05% Triton per well. As a standard 156-10,000 pg/ml human TREM2-Fc (R&D Systems) was added to the plates, as well as diluted plasma samples in binding buffer (PBS + 1% BSA). Plates containing samples and standard were incubated at RT for 1 hour. The plates were washed thrice with a plate washer and 300 µL PBS + 0.05% Triton per well. Biotinylated goat anti-human TREM2 polyclonal antibody (R&D Systems) was added at 1:2,000 dilution in binding buffer and incubated for 1 hour at RT. The plates were washed thrice with a plate washer and 300 µL PBS + 0.05% Triton per well. Streptavidin-HRP (1:200 in binding buffer, R&D

Systems) was added to the plates and incubated for 20–30 minutes at RT. The plates were washed thrice with a plate washer and 300 µL PBS + 0.05% Triton per well. 100 µL TMB substrate solution was added and incubated until color developed. The reaction was stopped by adding 50 µL of 2N sulfuric acid and the plate was read in a Synergy H1 plate reader at 450 and 630 nm. Data were analyzed using GraphPad Prism.

Results

[0458] The half-life of AL2p variant antibodies was measured in human TREM2 Tg mice (**Table 11**). After injection of AL2p variant antibody, levels of sTREM2 significantly decreased down to 65% of control levels and remained low for at least 6 days (**Table 11**). It is unclear what causes this decrease. It could either be caused by AL2p blocking shedding of sTREM2 or by AL2p causing internalization of TREM2 after inducing clustering. And these data suggest that sTREM2 levels in plasma or CSF can be used as indicators for peripheral or brain target engagement in vivo in patients.

Table 11: Parameters measured in vivo in human TREM2 Tg mice for control huIgG1 and AL2p affinity matured variant antibodies

Antibody	Estimated half-life (days)	Plasma sTREM2 as % of baseline on day 6
Control huIgG1	14.6	99.97
AL2p-60 huIgG1 PSEG	1.5	51.75
AL2p-47 huIgG1	2.8	73.37
AL2p-58 huIgG1	4.6	43.70

Example 5: Production and Testing of Fc mutant variants of TREM-2 agonistic antibodies

Materials and Methods

Production of Fc mutant antibodies

[0459] Fc mutant antibodies were produced recombinantly via transient transfection of HEK cells, and purification via Protein-A affinity capture and size exclusion chromatography (SEC) polishing.

BWZ Reporter Assay

[0460] In addition to the BWZ reporter assays described in Examples 2 and 3, reporter cell assays for Fc-mutants were also carried out in co-culture with various FcgR-expressing cell lines such as THP-1 or Raji. In this case, the assay was modified to include 10^5 each of the reporter cell line as well as the FcgR-expressing line, in the same final volume of media (100 µL per well). The two cell types were counted on a Vi-CELL XR (Beckman Coulter) and mixed in reporter cell media (DMEM + 10% FBS) immediately prior to aliquoting into 96 well plates and addition of antibody. The assay was then carried out in the same manner as described previously (6 hour incubation with antibody at

37°C, followed by detection of luciferase with the ONE-GLO reagent (Promega) and a BioTek plate reader).

Complement (C3b) deposition assay

[0461] The ability of anti-TREM2 antibodies to drive complement deposition was measured on a stable HEK cell line overexpressing human TREM2 and DAP12, as well as on primary cells (monocyte-derived DCs). TREM2-expressing cells were diluted to $10^{\wedge 5}$ cells per 70 µL in media (DMEM+10% FBS for HEK, RPMI for DCs) and 70 µL of cells aliquoted per well in round-bottom 96 well plates (Falcon #351177). To these cells was added 10uL of 10x antibody diluted in the same media. Cells + antibody were incubated at 37°C for 30min, then 20 µL of pooled complement human serum (Innovative Research, IPLA-CSER) was added per well as a complement source and the plates incubated for a further 2 hours at 37°C. Afterwards, the cells were washed 2x with FACS buffer (PBS + 2% FBS + 1mM EDTA), and 100 µL of 1:50 diluted anti-C3b-APC antibody (Biolegend 846106) was added per well and incubated on ice for 30 minutes. The cells were then washed 2x with FACS buffer and resuspended in 50 µL/well of FACS buffer + 0.25 µL/well of propidium iodide (Fischer Scientific, BD 556463 prior to analysis on an iQue flow cytometer (IntelliCyt).

Production of Fc-gamma-receptor detection reagents

[0462] Human and mouse FcgR detection reagents were designed by fusing the extracellular domain of each FcgR with the C-terminal addition of an AVI/His tag to facilitate site-specific biotinylation and purification (Boesch et al, 2014). AVI-His FcgRs were produced by transient transfection of HEK cells via and purified via immobilized metal affinity chromatography (IMAC) capture followed by size exclusion chromatography (SEC) for polishing. Purified FcgRs were biotinylated according to the conditions of the BirA biotin-protein ligase bulk reaction kit (Avidity). Tetrameric FcgR reagents were prepared immediately prior to use by mixing 1ug/mL of FcgR with a $1/4^{th}$ molar ratio of streptavidin-APC (eBioscience 17-4317-82) in FACS buffer and incubating for 10min with rotation.

Fc-gamma-receptor binding assay

[0463] The ability of antigen-bound antibody to engage Fc receptors was measured on the stable TREM2/DAP12 expressing HEK cell line. Briefly, TREM2-expressing cells were diluted to 100k cells per 90 µL in media (DMEM+10% FBS for HEK) and 90uL of cells aliquoted per well in round-bottom 96 well plates (Falcon). To these cells was added 10 µL of 10x antibody diluted in the same media. Cells + antibody were incubated at 37°C for 1h to opsonize target cells, then the cells were washed 2x in FACS buffer, and 100uL of the tetrameric FcgR detection reagent of FACS buffer were added per well. Opsonized cells were incubated with FcgR tetramers for 1h at 4°C, and the cells were washed 2x with FACS buffer and resuspended in FACS buffer prior to analysis on an iQue flow cytometer (IntelliCyt).

Results

[0464] In the following example the sequence FC1 (human IgG1 G1m 17,1) was used as the parental human IgG1 Fc and sequence FC10 was used as the parental human IgG2 Fc for all further modifications.

[0465] Self-clustering Fc mutants that induce strong complement responses also may drive an agonistic response by inducing clustering (*e.g.*, by inducing antibody multimerization), which can activate receptors; however, such mutants may also target the complement system towards the very target cells from which the beneficial activity is being elicited. Therefore, combinations of Fc mutants were tested for ability to retain the beneficial effects of clustering (*e.g.*, hexamer-forming mutants) while reducing complement dependent cytotoxicity (CDC), for example by reducing the monomeric affinity to C1q.

[0466] Combinations of E430G with Fc mutants (*e.g.*, K322A, A330S and P331S), which can reduce complement activation; as well as with other Fc mutants (*e.g.*, combinations of L234A, L234F, L235A, L235E, and A330L) that reduce binding to activating Fc-gamma-receptors (Armour et al, 2003; Idusogie et al, 2001) were tested in the context of anti-TREM2 antibody binding.

BWZ Reporter Assay

[0467] Using the reporter-cell assay agonistic ability of the resulting antibodies was evaluated as well as their ability to drive complement activation through CDC and C3b-deposition assays. E430G Fc variants of an anti-TREM2 antibody strongly enhance agonistic activity, even in the presence of compensatory mutations to remove C1q binding, such as P331S (**FIG. 1A**). To further probe these results, the ability of anti-TREM2 antibodies to activate TREM2 in the presence of cell types bearing Fc gamma receptors was tested. Fc-gamma-receptor dependent clustering may be an important mechanism for the activity of these antibodies in vivo, and as such should be retained if possible. In a co-culture system with THP-1 cells (ATCC® TIB-202™), a monocytic leukemia cell line expressing several Fc gamma receptors, enhanced TREM2 signaling activity was seen from the humanized IgG1 variant (**FIG. 1B**). Adding in the E430G mutation further enhanced the activity, showing a possible additive or synergistic effect of these two mechanisms. However, adding in compensatory mutations to fully remove Fc-receptor binding, such as LALAPS (L234A, L235A, P331S), also removed much of the benefit of using E430G in this system.

Complement (C3b) deposition assay

[0468] E430G mutant can cause a strong increase in C3b deposition and CDC, over the parental IgG1. This increase could be ameliorated following the addition of compensatory mutations such as LALAPS (**FIG. 2A**). Various Fc mutant combinations of K322A, A330S and P331S together with E430G were tested for their ability to retain agonistic functionality (including through FcgR-based mechanisms) while reducing complement activation. Inclusion of P331S alone with E430G (PSEG) was sufficient to reduce complement activation below the level of that induced by the parental IgG1 in one affinity-matured AL2p variant (**FIG. 2B**), while K322A and A330S had limited effect even in combination with P331S.

Fc-gamma-receptor binding assay

[0469] Fc mutant variants of AL2p leads are also tested for their ability to engage Fc-gamma-receptors. In this assay TREM-2 expressing cells are opsonized with anti-TREM2 antibodies and then a tetramerized FcgR/streptavidin-APC probe is used to evaluate their ability to engage FcgRs. Both mouse and human FcgRs are tested.

Example 6: Improved binding of affinity matured TREM2 antibodies to BW cells expressing human TREM2

Materials and Methods

[0470] *Binding assay*: FACS-based cell binding was performed as described in Example 2.

Results

[0471] Side-by side comparison in binding was performed of the chimeric parental AL2p antibody as huIgG1 and various humanized and affinity matured variants thereof on either huIgG1 or huIgG1 PSEG Fc. AL2p-58 and AL2p-61 show a 2 to 3.6 fold increase in apparent affinity, while there is not great affinity improvement by AL2p-37 and AL2p-47 on cell expressed TREM2, despite both antibodies showing increased affinity to recombinant TREM2 (**Table 12**).

Table 12: Cell-based binding assay of high affinity binding of 9F5 affinity matured variants

Antibody ID	Fc isotype	Kd (nM)	Bmax (MFI)
AL2p	huIgG1	1.32	199026
AL2p-58	huIgG1	0.63	196455
AL2p-58	huIgG1 PSEG	0.36	140225
AL2p-37	huIgG1	1.17	216292
AL2p-47	huIgG1	1.20	226371
AL2p-61	huIgG1	0.42	210636

Example 7: Improved soluble and plate bound TREM2 signaling activation upon affinity maturation of AL2p

Materials and Methods

[0472] *Luciferase assay*-The ability of plate-bound or soluble, full-length anti-TREM2 antibodies to activate human TREM2-dependent genes was evaluated using a luciferase reporter assay as described in Example 3.

Results

[0473] The ability of AL2p variant antibodies to activate TREM2-mediated signaling was tested in a heterologous NFAT:luciferase system. BW cells express human TREM2/DAP12 chimera, as well as a NFAT:luciferase reporter gene that is activated upon TREM2 clustering either by natural ligands or TREM2 antibodies. Compared to AL2p, which had little stimulatory activity when plate bound, all affinity matured AL2p offspring, except for AL2p-37, showed dramatic improvement in plate bound signal activation, up to 10-fold over AL2p for AL2p-58 huIgG1 PSEG (**Table 13**). A similar

improvement was observed for signaling activation by soluble IgG, where all affinity matured antibodies tested activated signaling with a reduced EC50 and increased signaling levels compared to AL2p.

Table 13: Activation of TREM2 signaling in NFAT:luciferase expressing BW cells

Antibody ID	Fc isotype	Plate bound IgG, fold over unstimulated control (25nM IgG)	Soluble IgG, EC50 (nM)	Soluble IgG, fold over control IgG (17nM IgG)
AL2p	huIgG1	1.29	14.59	4.51
AL2p-58	huIgG1	9.88	4.83	9.97
AL2p-58	huIgG1 PSEG	12.91	2.99	12.11
AL2p-37	huIgG1	1.56	9.41	7.63
AL2p-47	huIgG1	3.94	6.50	8.77
AL2p-61	huIgG1	8.97	5.24	10.75

Example 8: AL2p variants block production of sTREM2 by primary human dendritic cells *in vitro*

Materials and Methods

[0474] *Generation of human dendritic cells and treatment with TREM2 antibodies*-Human monocytes were isolated from whole blood using RosetteSep Human monocyte enrichment cocktail (Stemcell technologies) and Ficoll centrifugation per manufacturer protocols. After lysing red blood cells with ACK lysing buffer, monocytes were resuspended in complete media (RPMI, 10% FBS, Pen/Strep, L-glutamine, HEPES, non-essential amino acid, Sodium pyruvate) with 100 ng/ml human GM-CSF (hu-GMCSF) and human IL-4 (hu-IL-4) to differentiate dendritic cells for 6 days.

[0475] All suspended dendritic cells were harvested and tested for CD11c expression by FACS staining Briefly, cells were washed in FACS buffer (PBS + 2% FBS) and incubated with 1:5 dilution of anti-human CD11c-FITC or isotype control-FITC (BD Biosciences) for 1hr on ice. Cells were washed with 2ml FACS buffer, pelleted by centrifugation and 250ul FACS buffer was added and cells were analyzed with a BD FACS Canto. For both donors tested, >90% of cells were CD11c positive and thus differentiated to human dendritic cells.

[0476] Harvested DC's were washed with PBS to remove cytokines, counted and plated at 100,000 cells/well in complete RPMI media in 96 well plates at 50ul. Cells were incubated at 37C for one hour to let them settle and to block the plate with serum albumin. Thereafter, 50ul of 2x antibody titrations in RPMI were added to the plates. Cells were incubated for 48h.

[0477] Cell supernatant was harvested to measure sTREM2. PBS + 3mM EDTA was added to the plates. Plates were incubated at 37C for 5-10 minutes, until cells would go into suspension upon pipetting. Cells were transferred to 96 well U-bottom plates, pelleted by centrifugation and resuspended in 45ul FACS buffer and analyzed on iQE. Relative cell numbers were measured by counting the number of cells in a fixed volume of FACS buffer. Data were analyzed using Microsoft Excel and GraphPad Prism.

[0478] *TREM2 MSD assay*-A human TREM2-specific MSD assay was developed. The capture anti-TREM2 antibody T2KO811 was plated at 1 μg/ml in PBS overnight at 4C (25 μL per well in single spot MSD plates, Meso Scale Discovery). The plates were washed thrice with a plate washer and 150 μL PBS + 0.05% Triton per well. As a standard 100-0.02 ng/ml human TREM2-Fc (R&D Systems) was added to the plates, as well as cell supernatant diluted in binding buffer (PBS + 1% BSA), all at 50ul per well. Plates containing samples and standard were incubated at RT for 1 hour. The plates were washed thrice with a plate washer and 150 μL PBS + 0.05% Triton per well. Biotinylated goat anti-human TREM2 polyclonal antibody (R&D Systems) was added at 1:2,000 dilution in binding buffer and incubated for 1 hour at RT. The plates were washed thrice with a plate washer and 150 μL PBS + 0.05% Triton per well. 25μl sulfo-tag conjugated Streptavidin (0.2μg/ml in binding buffer, MesoScale Discovery) was added to the plates and incubated for 20 min at RT. The plates were washed thrice with a plate washer and 150 μL PBS + 0.05% Triton per well. 150μl of 1x Read Buffer (MesoScale Discovery) was added to each well and plates were read on a Sector Imager (MesoScale Discovery). Data were analyzed in Excel and Graph Pad Prism. It was tested whether AL2p lineage antibodies interfere with the assay, by spiking the MSD assay with different concentrations of AL2p variant antibodies. This had no effect on signal levels measured, suggesting that there is no assay interference by AL2p variant antibodies.

Results

[0479] TREM2 is produced as a cell surface receptor that can be cleaved to release the extracellular domain. A rare TREM2 mutation in humans (H157Y) causes increased production of sTREM2 and increases the risk of development of late onset Alzheimer's disease (Thornton et al, EMBO Mol Med 2017, 9(10): 1366-78).

[0480] To test whether TREM2 antibodies block shedding of the receptor, sTREM2 secreted into the media by primary human dendritic cells over the course of 48h was measured by ELISA. Dendritic cells derived from monocytes of two human blood donors were tested, donor 534 and 535. The average concentration of sTREM2 for donor 534 was 97.0 ng/ml and for donor 535 72.5 ng/ml. Upon addition of TREM2 antibodies sTREM2 secretion decreased with increasing antibody concentrations (**FIG.5A** and **FIG.5B**). The weakest effect was observed by the parental AL2p antibody as a huIgG1 chimera, although it did significantly reduce sTREM2 level at higher antibody concentrations in both donors. The humanized, affinity matured variant AL20-58 either as huIgG1 WT or PSEG showed the strongest decrease at the lowest antibody concentration. Results were similar across the two donors.

[0481] To test whether the reduction in sTREM2 was due to cell death and therefore reduction in cell numbers, cell density after antibody incubation was measured using iQE FACS analysis. There was no change in cell numbers upon treatment of dendritic cells with TREM2 antibodies in neither of the two donors (**FIG.6A** and **FIG.6B**).

Example 9: TREM2 agonistic antibodies increase viability of primary human macrophages and dendritic cells

Methods

[0482] Human monocytes from three different donors were isolated from whole blood using RosetteSep Human monocyte enrichment cocktail (Stemcell technologies) and Ficoll centrifugation per manufacturer protocols. After lysing red blood cells with ACK lysing buffer, monocytes were resuspended in complete media (RPMI, 10% FBS, Pen/Strep, L-glutamine, HEPES, non-essential amino acid, Sodium pyruvate). For dendritic cell differentiation, 100 ng/ml human GM-CSF (hu-GMCSF) and human IL-4 (hu-IL-4) were added to the monocyte culture for six days. For macrophage differentiation, 100 ng/ml human M-CSF (huM-CSF) was used instead.

[0483] For plate bound antibodies, one day before, 10 μg/ml anti-TREM2 or control antibodies were added into a 96 well plate and left at 4°C overnight. The next day, the plate was washed twice with PBS. Cells were plated at 25000 cells/well without additional cytokines for human DCs and macrophages, and cultured for 2 days. For soluble antibody conditions, antibodies were added to the media when the cells are plated. Cell viability was quantified using the CellTiter-Glo Luminescent cell viability kit (Promega) per manufacturer's protocol and luminescence was measured using a Biotek Synergy H1 plate reader. Data were analyzed using Microsoft Excel and GraphPad Prism.

Results

[0484] Both the parental AL2p antibody and its affinity matured offspring were tested for their ability to promote survival of primary human dendritic cells and macrophages. Cells were added to plates containing a titration of plate bound antibodies, incubated for 48 hours and viability was evaluated by measuring ATP content of the cells using CellTiterGlo (Promega).

[0485] Compared to the isotype control antibody, stimulating cells with TREM2 antibodies increased viability of both primary human macrophages and dendritic cells in a dose dependent manner (**FIG. 8A** and **FIG. 8B**). Compared to the parental AL2p antibody, all affinity matured variants showed up to a several hundred-fold increase in efficacy, as evidenced by reduced half-maximal activity (see EC50 values in **Table 14** (EC50 values (nM) for different TREM2 antibodies in promoting viability of primary human macrophages or dendritic cells from three different donors (D558- 560). P.F. denotes poor curve fit. All antibodies were tested as huIgG1, with AL1p-58 also being tested as huIgG1 PSEG.)). The parental AL2p antibody does show a dose dependent increase in viability, however, affinity matured versions of the antibody, especially AL2p-58 (both as huIgG1 and huIgG1 PSEG), AL2p-47 and AL2p-60, show several hundred-fold lower EC50, suggesting a much higher potency. AL2p-37 still showed a reduced EC50 compared to the parental IgG, but it is of lower potency than the other antibodies.

[0486] In addition, the ability of antibody AL2p-58 to increase viability in soluble format was evaluated in a similar assay, but the antibody was added to the media when the cells were plated.

Compared to isotype control antibody, AL2p-58 was able to increase viability of both primary human macrophages and dendritic cells (**FIG.8C-8F**). These results suggest that antibody AL2p-58 will be functionally active *in vivo*.

Table 14

	Macrophages			Dendritic cells		
Antibody	**D558**	**D559**	**D560**	**D558**	**D559**	**D560**
AL2p	12.267	146.067	128.667	95.733	41.180	55.120
AL2p-58	0.005	0.359	0.469	0.288	0.341	0.271
AL2p-58 PSEG	0.001	0.322	0.426	0.206	0.276	0.206
AL2p-47	0.013	1.557	1.247	1.017	1.131	0.672
AL2p-60	P.F.	0.194	0.154	0.152	0.244	0.178
AL2p-37	1.235	18.313	31.827	4.187	6.155	4.472

Example 10: AL2p variants reduce levels of plasma sTREM2 levels *in vivo*

Methods

[0487] *In vivo procedures*-Human TREM2 BAC Tg mice were group-housed in polycarbonate cages and acclimated for at least 5 days prior to commencing studies. Animals were maintained in a 12 hr light/dark cycle with room temperature maintained at 22±2°C and approximately 50% humidity, and received food and water *ad libitum*. For Experiments I-III animals were injected I.P. or I.V. with AL2p-47 huIgG1, AL2p-47 huIgG1 ASPSEG, AL2p-58 huIgG1, AL2p-58 huIgG1 PSEG, AL2p-61 huIgG1 PSEG or control huIgG1 on day 0 and blood for plasma was collected in heparinized tubes 2-4 days prior to study initiation and on Days 0 (4 hrs after injections), 1, 3, 6, 10 and 14. For Experiment IV, either AL2p msIgG1, T-21-9 msIgG1 or control msIgG1 were injected at 20mg/kg I.P. on day 0 and plasma was collected on days 0 (4h after injection), 2, 5, 8 and 14. Plasma was isolated by spinning blood samples for 5 minutes at 5,000 rpm then collecting the supernatant. A total of four in vivo experiments were performed: experiment I: n=3 animals/group; experiment II: n=10 animals/group; experiment III: n=4 animals/ group; experiment IV: n=4 animals/group.

[0488] *Human TREM2 MSD assay*-Plasma sTREM2 was measured by MSD as outlined in Example 8.

Results

[0489] Affinity matured variants of AL2p were tested for their ability to reduce sTREM2 levels, based on in vitro experiments shown in Example 8 that suggest AL2p antibodies block TREM2 shedding either directly by blocking binding of the ADAM sheddase or indirectly by inducing TREM2 signal activation and endocytosis. Human TREM2 expressing BAC Tg mice were injected with 15mg/kg IgG on day 0 and sTREM2 levels were monitored over the course of 14 days and normalized to pre-treatment baseline. **Table 15** outlines the % reduction in plasma sTREM2 observed

after treatment with the different AL2p variants and **FIG.7A-C** show graphs depicting reduction in sTREM2 after treatment of human BAC Tg mice with affinity matured versions of AL2p. In contrast, parental AL2p had no significant effect on plasma sTREM2 levels **(FIG.7D)**, while another TREM2 antibody that binds the Ig domain of the protein (T21-9) causes a several fold elevation of plasma sTREM2, likely because it stabilizes the protein. All variants induced reduction of sTREM2 for several days after treatment. AL2p-58 huIgG1 PSEG induced the strongest and longest lasting downregulation of sTREM2. These data suggest that sTREM2 in both plasma and CSF can be used as a marker for target engagement in vivo in human patients.

Table 15: Reduction in plasma sTREM2 after treatment with AL2p variant antibodies

Antibody	huIgG1	Expt. #	4h, day 0	Day 1	Day 3	Day 6	Day 10	Day 14
AL2p-47	WT	I	102.9	88.3	74.6*	73.4**	87.7**	82.3
		III	89.7	92.9	83.6*	91.5**	111.5	133.0
AL2p-47	ASPSEG	III	103.1	107.5	93.5	97.5*	127.7	150.8
AL2p-58	WT	I	86.3	62.3****	45.0****	43.7****	67.7****	93.2
		II		85.0*	56.7****	54.0****	94.8	100.9
		III	98.5	85.8*	58.0****	59.4****	79.9****	131.9
AL2p-58	PSEG	II		62.8****	46.2****	46.2****	90.2*	113.2
AL2p-61	PSEG	I	74.2	57.8****	47.4****	51.8****	98.2	88.2

Shown is % sTREM2 found in plasma of human TREM2 BAC Tg mice treated with different TREM2 antibody variants either as huIgG1 WT or huIgG1 PSEG or huIgG1 ASPSEG. Stars indicate values that are significantly lower compared to control huIgG1 injected mice (*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001) using Two-way ANOVA and post hoc test for pairwise comparisons.

Example 11: AL2p variants *in vivo*

Methods

[0490] 8 week old C57BL/6 (WT) or Bac-TG-hTREM2 mice were injected i.p. with 3 ml of 3% thioglycollate. After 3 days, when the peritoneal cavity was enriched with peritoneal macrophages ($CD11b^+F4/80^+$ expressing TREM2, mice were injected with huIgG1 or TREM2-specific antibodies AL2p-58 huIgG1 or AL2p-58 huIgG1 (40mg/kg). Peritoneal cells were recovered after one hour and immediately lysed in lysis buffer (n-dodecyl-b-malthoside 1%, 50 Mm Tris-HCl (pH 8.0), 150 mM NaCl, 1 mM EDTA, 1.5 mM $MgCl_2$, 10% glycerol, plus protease and phosphatase inhibitors), split after lysis and immunoprecipitated with rat anti-h/m TREM2 (RD, clone 237920) or isotype control. Precipitated proteins were fractionated by SDS-PAGE (non-reducing conditions), transferred to nitrocellulose membranes and probed with anti-phosphotyrosine antibody (Millipore, 4G10). To confirm that each cell lysate used for TREM2 immunoprecipitations contained equal amount of proteins, an equal amount of lysates were collected before immunoprecipitation and fractionated by SDS-PAGE (reducing conditions). Immunoblots were probed with antibodies directed against human TREM2 (R&D #AF1828).

Results

[0491] TREM2 ligand binding induces receptor clustering, which triggers phosphorylation of its adaptor protein Dap12 and an intracellular signaling cascade. To test if AL2p variant antibodies induce TREM2 signal activation *in vivo*, WT or human TREM2 expressing Bac-Tg mice were treated with thioglycollate to recruit macrophages to the peritoneum. After three days, mice were injected with anti-TREM2 or control huIgG1 antibodies and subsequently, peritoneal macrophages were harvested, lysed and phosphorylation of Dap12 associated with TREM2 was probed as a measure of TREM2 signaling activation.

[0492] Treatment of Bac-Tg mice with AL2p-58 huIgG1 or AL2p huIgG1 PSEG caused a strong increase in Dap12 phosphorylation compared to control huIgG1 (**FIG. 9**). In contrast, the TREM2 antibodies showed no effect on Dap12 in WT mice, since these antibodies are not murine cross-reactive. These results demonstrate that AL2p-58 antibodies can cluster and activate the TREM2 receptor *in vivo*.

Example 12: Unspecific reactivity of AL2p variants

Methods

[0493] A FACS-based assay to measure polyspecific reactivity (PSR) was performed as described in Xu et al., Protein Engineering, Design and Selection, 2013, 26 (10), 663-70.

Results

[0494] While the parental humanized versions of AL2p (AL2p-h50, AL2p-h77) were PSR low, indicating that they do not unspecifically bind to non-TREM2 targets, upon increasing affinity to TREM2 by affinity maturation, AL2p antibody variants showed elevated PSR values (**Table 16**). PSR positively correlates with affinity and higher unspecific binding, which can result in faster elimination of circulating antibody from the body and thus a shorter half-life. The results in **Table 16**, when combined with those in **Tables 9A-9C**, **10A-10C**, **11**, **13** and **14** indicate that AL2p antibody variants with a high PSR have too short a half-life and AL2p antibody variants with low PSR do not exhibit sufficient functionality. However, AL2p antibody variants with medium PSR exhibit both low unspecific binding and better functionality than AL2p antibody variants with low PSR (**Tables 9A-9C**, **10A-10C**, **13** and **14**).

Table 16: Summary of PSR reactivity of AL2p variant antibodies

Antibody	PSR value	PSR range
AL2p-h50	0.01	Low
AL2p-h77	0.09	Low
AL2p-2	0.10	Low
AL2p-3	0.05	Low
AL2p-4	0.10	Low
AL2p-5	0.15	Low
AL2p-6	0.10	Low
AL2p-7	0.74	High
AL2p-8	0.82	High
AL2p-9	0.80	High

Antibody	PSR value	PSR range
AL2p-10	0.14	Low
AL2p-11	0.68	High
AL2p-12	0.57	Medium
AL2p-13	0.71	High
AL2p-14	0.80	High
AL2p-15	0.34	Medium
AL2p-16	0.84	High
AL2p-17	0.77	High
AL2p-18	0.72	High
AL2p-19	0.84	High
AL2p-20	0.74	High
AL2p-21	0.75	High
AL2p-22	0.88	High
AL2p-23	0.70	High
AL2p-24	0.85	High
AL2p-25	0.80	High
AL2p-26	0.80	High
AL2p-27	0.87	High
AL2p-28	0.52	Medium
AL2p-29	0.72	High
AL2p-30	0.70	High
AL2p-31	0.85	High
AL2p-32	0.10	Low
AL2p-33	0.05	Low
AL2p-35	0.10	Low
AL2p-36	0.82	High
AL2p-37	0.15	Low
AL2p-38	0.73	High
AL2p-39	0.66	High
AL2p-40	0.69	High
AL2p-41	0.77	High
AL2p-42	0.76	High
AL2p-43	0.70	High
AL2p-44	0.67	High
AL2p-45	0.33	Medium
AL2p-46	0.44	Medium
AL2p-47	0.48	Medium
AL2p-48	0.55	Medium
AL2p-49	0.54	Medium
AL2p-50	0.16	Low
AL2p-51	0.20	Low
AL2p-52	0.14	Low
AL2p-53	0.22	Low
AL2p-54	0.38	Medium
AL2p-55	0.37	Medium
AL2p-56	0.37	Medium
AL2p-57	0.42	Medium
AL2p-59	n.d.	
AL2p-61	0.74	High
AL2p-62	0.19	Low
AL2p-58	0.59	Medium

SEQUENCES

Human TREM2 protein (SEQ ID NO: 1)
MEPLRLLILLFVTELSGAHNTTVFQGVAGQSLQVSCPYDSMKHWGRRKAWCRQLGEKGPCQ
RVVSTHNLWLLSFLRRWNGSTAITDDTLGGTLTITLRNLQPHDAGLYQCQSLHGSEADTLRK
VLVEVLADPLDHRDAGDLWFPGESESFEDAHVEHSISRSLLEGEIPFPPTSILLLLACIFLIKILA
ASALWAAAWHGQKPGTHPPSELDCGHDPGYQLQTLPGLRDT

Mouse TREM2 protein (SEQ ID NO: 2)
MGPLHQFLLLLITALSQALNTTVLQGMAGQSLRVSCTYDALKHWGRRKAWCRQLGEEGPC
QRVVSTHGVWLLAFLKKRNGSTVIADDTLAGTVTITLKNLQAGDAGLYQCQSLRGREAEVL
QKVLVEVLEDPLDDQDAGDLWVPEESSSFEGAQVEHSTSRNQETSFPPTSILLLLACVLLSKF
LAASILWAVARGRQKPGTPVVRGLDCGQDAGHQLQILTGPGGT

Rat TREM2 protein (SEQ ID NO: 3)
MEPLHVFVLLLVTELSQALNTTVLQGVAGQSLRVSCTYDALRHWGRRKAWCRQLAEEGPC
QRVVSTHGVWLLAFLRKQNGSTVITDDTLAGTVTITLRNLQAGDAGLYQCQSLRGREAEVL
QKVVVEVLEDPLDDQDAGDLWVPEESESFEGAQVEHSTSSQVSSCGSPLTYHLPPKEPIRKDL
LPTHFHSSPPGLCPPEQASYSQHPLGCGQGQAEAGDTCGQWARL

Rhesus monkey TREM2 protein (SEQ ID NO: 4)
MPDPLFSAVQGKDKILHKALCICPWPGKGGMEPLRLLILLFATELSGAHNTTVFQGVEGQSL
QVSCPYDSMKHWGRRKAWCRQLGEKGPCQRVVSTHNLWLLSFLRRRNGSTAITDDTLGGT
LTITLRNLQPHDAGFYQCQSLHGSEADTLRKVLVEVLADPLDHRDAGDLWVPGESESFEDAH
VEHSISRSLLEGEIPFPPTSVLLLLACIFLIKILAASALWAAAWHGQKPGTHPPSEPDCGHDPGH
QLQTLPGLRDT

Cynomolgus monkey TREM2 protein (SEQ ID NO: 5)
MEPLRLLILLFATELSGAHNTTVFQGVEGQSLQVSCPYDSMKHWGRRKAWCRQLGEKGPCQ
RVVSTHNLWLLSFLRRRNGSTAITDDTLGGTLTITLRNLQPHDAGFYQCQSLHGSEADTLRK
VLVEVLADPLDHRDAGDLWVPGESESFEDAHVEHSISRSLLEGEIPFPPTSVLLLLACIFLIKIL
AASALWAAAWHGQKPGTHPPSEPDCGHDPGHQLQTLPGLRDT

Equine TREM2 protein (SEQ ID NO: 6)
MEPLPLLILLSVAELSRGHNTTVFQGTAGRSLKVSCPYNSLMHWGRRKAWCRQLGEDGPCQ
QVVSTHSLWLLSFLKRRNGSTVITDDALGGILTITLRNLQAHDAGFYQCQSLHGGEADTLRK
VLVEVLADPLDHQEPGDLWIPKESESFEDAQVEHSISRSLVEEEIPSLPTSILLLLACIFLSKLLA
ASAIWAAAWHGQKQETPPASEPDRGHDPGYQLHTLTGERDT

Pig TREM2 protein (SEQ ID NO: 7)
METLGLLLLLWVAELSRAHNTSVFQGTAGQSLRVSCSYNSLKHWGRRKAWCRQLSEEGLC
QHVVSTHPTWLLSFLKRRNGSTAITDDALGGTLTITLRNLQAHDAGLYQCQSLHGSEADTLK
KVLVEVLADPLESQSKSFQDVQMEHSISRNLSEESLFPPTSTLFLLACVFLSKLLVASALWAA
AWHGHKQRTSPAGGLDCGRDPGDQDQTLTDELGESSDQDQTLTELRDT

Dog TREM2 protein (SEQ ID NO: 8)
MEPLWLLILLAVTELSGAHNTTVFQGMAGRSLQVSCPYNSLKHWGRRKAWCRQVDKEGPC
QRVVSTHRSWLLSFLKRWNGSTAIVDDALGGTLTITLRNLQAHDAGLYQCQSLYGDEADTL
RKVLVEVLADPLDHLDPGDLWIPEESKGFEDAHVEPSVSRSLSEEEIPFPPTSILFLLACIFLSKF
LAASALWAAAWRGQKLGTPQASELDCSCDPGYQLQTLTEPRDM

Parental mouse AL2p heavy chain variable region (SEQ ID NO: 119)
QVQLQQSGPELVKPGASLKISCKASGYAFSSSWMNWVKQRPGKGLEWIGRIYPGDGDTNYN
GEFRVRATLTADTSSTTAYMQLSSLTSEDSAVYFCARLLRNQPGESYAMDYWGQGASVTVS
S

Parental mouse AL2p light chain variable region (SEQ ID NO: 120)
DVVMTQTPLSLPVSLGDQASISCRSSQSLVHSNGYTYLHWYLQKPGQSPKLLIYKVSNRFSG
VPDRFSGSGSGTDFTLKISRVEADDLGVYFCSQSTRVPYTFGGGTKLEIK

FC1 (wild-type human IgG1) (SEQ ID NO: 146)
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPGK

FC2 (IgG1 E430G) (SEQ ID NO: 147)
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HGALHNHYTQKSLSLSPGK

FC3 (IgG1 L234A, L235A, P331S: LALAPS) (SEQ ID NO: 148)
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLF
PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS
VLTVLHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPGK

FC4 (IgG1 L234A, L235A, P331S, E430G: LALAPSEG) (SEQ ID NO: 149)
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLF
PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS
VLTVLHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHGALHNHYTQKSLSLSPGK

FC5 (IgG1 K322A, E430G: KAEG) (SEQ ID NO: 150)
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV
LTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HGALHNHYTQKSLSLSPGK

FC6 (IgG1 P331S, E430G: PSEG) (SEQ ID NO: 151)
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC

LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HGALHNHYTQKSLSLSPGK

FC7 (IgG1 A330S, P331S, E430G: ASPSEG) (SEQ ID NO: 152)
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPSSIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCL
VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH
GALHNHYTQKSLSLSPGK

FC8 (IgG1 K322A, P331S, E430G: KAPSEG) (SEQ ID NO: 153)
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV
LTVLHQDWLNGKEYKCAVSNKALPASIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HGALHNHYTQKSLSLSPGK

FC9 (wild-type human IgG2) (SEQ ID NO: 154)
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTV
VHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVK
GFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK

FC10 (IgG2 E430G) (SEQ ID NO: 155)
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTV
VHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVK
GFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHGA
LHNHYTQKSLSLSPGK

FC11 (IgG2 A330S P331S E430G: ASPSEG) (SEQ ID NO: 156)
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTV
VHQDWLNGKEYKCKVSNKGLPSSIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVK
GFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHGA
LHNHYTQKSLSLSPGK

CLAIMS

What is claimed is:

1. 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: $YAFX_1X_2X_3WMN$, wherein X_1 is S or W, X_2 is S, L, or R, and X_3 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, X_2 is D or Q, X_3 is Q, R, H, W, Y, or G, X_4 is F, R, or W, and X_5 is Q, R, K, or H (SEQ ID NO: 122); and
an HVR-H3 comprising the sequence according to Formula III: $ARLLRNX_1PGX_2SYAX_3DY$, wherein X_1 is Q or K, X_2 is E, S, or A, and X_3 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).

2. 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: $RX_1SX_2SLX_3HSNX_4YTYLH$, wherein X_1 is S or T, X_2 is Q, R, or S, X_3 is V or I, and X_4 is G, R, W, Q, or A (SEQ ID NO: 127);
an HVR-L2 comprising the sequence according to Formula V: $KVSNRX_1S$, wherein X_1 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).

3. 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: $YAFX_1X_2X_3WMN$, wherein X_1 is S or W, X_2 is S, L, or R, and X_3 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, X_2 is D or Q, X_3 is Q, R, H, W, Y, or G, X_4 is F, R, or W, and X_5 is Q, R, K, or H (SEQ ID NO: 122); and
an HVR-H3 comprising the sequence according to Formula III: $ARLLRNX_1PGX_2SYAX_3DY$, wherein X_1 is Q or K, X_2 is E, S, or A, and X_3 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: $RX_1SX_2SLX_3HSNX_4YTYLH$, wherein X_1 is S or T, X_2 is Q, R, or S, X_3 is V or I, and X_4 is G, R, W, Q, or A (SEQ ID NO: 127); an HVR-L2 comprising the sequence according to Formula V: $KVSNRX_1S$, wherein X_1 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).

4. 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).

5. 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).

6. 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).

7. 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).

8. The antibody of any one of claims 1 to 7, wherein 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.

9. The antibody of any one of claims 1 to 8, wherein:

(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 KVSNRRS (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 KVSNRFS (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 KVSNRVS (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 KVSNRRS (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 KVSNRFS (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 KVSNRFS (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 KVSNRRS (SEQ ID NO: 134), and the HVR-L3 comprises the amino acid sequence SQSTRVPYT (SEQ ID NO: 129).

10. 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.

11. An antibody that binds to a TREM2 protein, wherein 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).

12. The antibody of claim 10 or claim 11, wherein:

(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.

13. The antibody of any one of claims 1-12, 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.

14. 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.

15. An antibody that binds to a TREM2 protein, wherein 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).

16. The antibody of any one of claims 1-15, wherein the antibody is of the IgG class, the IgM class, or the IgA class.

17. The antibody of claim 16, wherein the antibody is of the IgG class and has an IgG1, IgG2, IgG3, or IgG4 isotype.

18. The antibody of claim 17, wherein 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.

19. The antibody of claim 18, 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;

(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.

20. The antibody of any one of claims 1-19, wherein the TREM2 protein is human protein.

21. The antibody of claim 20, wherein the TREM2 protein is a wild-type protein.

22. The antibody of claim 20, wherein the TREM2 protein is a naturally occurring variant.

23. The antibody of any one of claims 1-22, wherein 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.

24. The antibody of claim 23, wherein the fragment is an Fab, Fab', Fab'-SH, F(ab')2, Fv or scFv fragment.

25. The antibody of any one of claims 1-24, wherein the antibody is a monoclonal antibody.

26. The antibody of any one of claims 1-7, 9, and 16-24, wherein the antibody is a humanized antibody.

27. The antibody of any one of claims 1-26, wherein 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.

28. The antibody of any one of the preceding claims, wherein the antibody binds specifically to both human TREM2 and cynomolgus monkey TREM2.

29. The antibody of claim 28, wherein 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.

30. The antibody of claim 28 or claim 29, wherein the antibody has a dissociation constant (K_D) for human TREM2 that ranges from about 9 μM to about 100 pM, or less than 100 pM, wherein the K_D is determined at a temperature of approximately 25°C.

31. The antibody of claim 28 or claim 29, wherein the antibody has a dissociation constant (K_D) for cynomolgus monkey TREM2 that ranges from about 50 nM to about100 pM, or less than 100 pM, wherein the K_D is determined at a temperature of approximately 25°C.

32. The antibody of any one of the preceding claims, wherein 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.

33. The antibody of any one of the preceding claims, wherein 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.

34. The antibody of any one of the preceding claims, wherein 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.

35. The antibody of any one of the preceding claims, wherein the antibody has an *in vivo* half-life that is lower than a human control IgG1 antibody.

36. The antibody of any one of the preceding claims, wherein 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.

37. The antibody of claim 36,wherein the antibody decreases plasma levels of soluble TREM2 *in vivo* by blocking cleavage, by inhibiting one or more metalloproteases, and/or by inducing internalization.

38. The antibody of any one of claims 1 to 37, wherein 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.

39. The antibody of any one of claims 1 to 37, wherein 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.

40. An antibody that binds to a TREM2 protein, comprising a heavy chain and a light chain, wherein:

(a) the heavy chain comprises the amino acid sequence of SEQ ID NO: 198, and the light chain comprises the amino acid sequence of SEQ ID NO: 214;

(b) the heavy chain comprises the amino acid sequence of SEQ ID NO: 199, and the light chain comprises the amino acid sequence of SEQ ID NO: 214;

(c) the heavy chain comprises the amino acid sequence of SEQ ID NO: 200, and the light chain comprises the amino acid sequence of SEQ ID NO: 214;

(d) the heavy chain comprises the amino acid sequence of SEQ ID NO: 201, and the light chain comprises the amino acid sequence of SEQ ID NO: 214;

(e) the heavy chain comprises the amino acid sequence of SEQ ID NO: 202, and the light chain comprises the amino acid sequence of SEQ ID NO: 215;

(f) the heavy chain comprises the amino acid sequence of SEQ ID NO: 203, and the light chain comprises the amino acid sequence of SEQ ID NO: 215;

(g) the heavy chain comprises the amino acid sequence of SEQ ID NO: 204, and the light chain comprises the amino acid sequence of SEQ ID NO: 215;

(h) the heavy chain comprises the amino acid sequence of SEQ ID NO: 205, and the light chain comprises the amino acid sequence of SEQ ID NO: 215;

(i) the heavy chain comprises the amino acid sequence of SEQ ID NO: 206, and the light chain comprises the amino acid sequence of SEQ ID NO: 216;

(j) the heavy chain comprises the amino acid sequence of SEQ ID NO: 207, and the light chain comprises the amino acid sequence of SEQ ID NO: 216;

(k) the heavy chain comprises the amino acid sequence of SEQ ID NO: 208, and the light chain comprises the amino acid sequence of SEQ ID NO: 218;

(l) the heavy chain comprises the amino acid sequence of SEQ ID NO: 209, and the light chain comprises the amino acid sequence of SEQ ID NO: 218;

(m) the heavy chain comprises the amino acid sequence of SEQ ID NO: 210, and the light chain comprises the amino acid sequence of SEQ ID NO: 218;

(n) the heavy chain comprises the amino acid sequence of SEQ ID NO: 211, and the light chain comprises the amino acid sequence of SEQ ID NO: 218;

(o) the heavy chain comprises the amino acid sequence of SEQ ID NO: 212, and the light chain comprises the amino acid sequence of SEQ ID NO: 217; or

(p) the heavy chain comprises the amino acid sequence of SEQ ID NO: 213, and the light chain comprises the amino acid sequence of SEQ ID NO: 217.

41. An isolated nucleic acid comprising a nucleic acid sequence encoding the antibody of any one of the preceding claims.

42. A vector comprising the nucleic acid of claim 41.

43. An isolated host cell comprising the vector of claim 42.

44. A method of producing an antibody that binds to TREM2, comprising culturing the cell of claim 43 so that the antibody is produced.

45. The method of claim 44, further comprising recovering the antibody produced by the cell.

46. An isolated antibody that binds to TREM2 produced by the method of claim 44 or claim 45.

47. A pharmaceutical composition comprising the antibody of any one of claims 1-40 and a pharmaceutically acceptable carrier.

48. 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 any one of claims 1-40.

49. The method of claim 48, wherein the disease, disorder, or injury is Alzheimer's disease.

50. 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.

51. The antibody of claim 50, 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.

52. The antibody of claim 50 or claim 51, 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.

53. The antibody of any one of claims 50 to 52, wherein the antibody induces one or more activities of a target specifically bound by the antibody.

54. The antibody of any one of claims 50 to 53, wherein the antibody binds to TREM2.