

## **ANTI-SIRP-BETA1 ANTIBODIES AND METHODS OF USE THEREOF**

### **CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit of priority of US Provisional Application No. 62/691,913, filed June 29, 2018, which is incorporated by reference herein in its entirety for any purpose.

### **FIELD OF THE PRESENT DISCLOSURE**

[0002] The present disclosure relates to anti-SIRP $\beta$ 1 antibodies and therapeutic uses of such antibodies.

### **BACKGROUND OF THE PRESENT DISCLOSURE**

[0001] Signal regulatory protein beta (SIRP $\beta$ ) belongs to the SIRP family of transmembrane receptors, which are expressed within the myeloid cell lineage (including monocytes, macrophages, granulocytes, and dendritic cells) and in neuronal cells. The SIRP family of proteins is characterized by an extracellular region containing 2 membrane-proximal IgC domains and a distal IgV domain. Unlike SIRP $\alpha$  receptors, SIRP $\beta$  proteins contain short cytoplasmic domains that lack cytoplasmic sequence motifs capable of recruiting protein tyrosine phosphatase SHP-2 and SHP-1. SIRP $\beta$ 1 isoform 1 associates with the adaptor protein DAP12, which contains a single cytoplasmic immunoreceptor tyrosine-based activating (ITAM) motif. *See, e.g.*, Dietrich et al. 2000, J Immunol 164:9-12; Liu et al. 2005 J Biol Chem 280:36132-36140. SIRP $\beta$  has been shown to be a microglial modulator of phagocytosis in Alzheimer's disease. *See, e.g.*, Gaikwad et al. 2009 Am J Pathol 175:2528-2539.

[0002] Accordingly, there is a need for therapeutic anti-SIRP $\beta$ 1 antibodies to treat disease, disorders, and conditions associated with SIRP $\beta$ 1 activity.

### **SUMMARY OF THE PRESENT DISCLOSURE**

[0003] In one aspect, the present disclosure refers to an isolated antibody that binds to human SIRP $\beta$ 1, wherein the antibody has at least one, at least two, at least three, at least four, or at least five properties selected from:

- a) binds to human SIRP $\beta$ 1 isoform 1, but does not bind to human SIRP $\alpha$ ;
- b) binds to human SIRP $\beta$ 1 isoform 1, but does not bind to human SIRP $\gamma$ ;
- c) binds to human SIRP $\beta$ 1 isoform 1, but does not bind to human SIRP $\beta$ 1 isoform 3;
- d) binds to human SIRP $\beta$ 1 isoform 1, but does not bind to mouse SIRP $\beta$ 1;
- e) binds to human SIRP $\beta$ 1 isoform 1, but does not bind to cynomolgus monkey SIRP $\beta$ 1 isoform 1;
- f) agonizes SIRP $\beta$ 1 activity on CD14-positive monocytes *in vitro* and/or *in vivo*;
- g) induces or increases respiratory burst in immune cells, such as neutrophils and/or monocytes *in vitro* and/or *in vivo*;
- h) induces or increases IL-8 expression in monocytes *in vitro* and/or *in vivo*;

- i) induces or increases TNF $\alpha$  expression in macrophages and/or dendritic cells *in vitro* and/or *in vivo*;
- j) induces neutrophil-mediated phagocytosis, for example, of tumor cells *in vitro* and/or *in vivo*;
- k) increases neutrophil-mediated tumor cell clearance *in vivo*;
- l) increases TREM2 expression on macrophages *in vitro* and/or *in vivo*;
- m) increases viability of macrophages *in vitro* and/or *in vivo*, alone and/or in combination with an agonist anti-TREM2 antibody; and
- n) increases viability of dendritic cells *in vitro* and/or *in vivo*.

**[0004]** In some examples, the antibody binds to human SIRP $\beta$ 1 isoform 1, but does not bind to human SIRP $\alpha$  or human SIRP $\beta$ 1 isoform 3. In some examples, the antibody binds to human SIRP $\beta$ 1 isoform 1, but does not bind to human SIRP $\alpha$ , SIRP $\gamma$ , or human SIRP $\beta$ 1 isoform 3. In some examples, the antibody has at least one, at least two, or at least three properties selected from:

- a) agonizes SIRP $\beta$ 1 activity on CD14-positive monocytes *in vitro* and/or *in vivo*;
- b) induces or increases respiratory burst in immune cells, such as neutrophils and/or monocytes *in vitro* and/or *in vivo*;
- c) induces or increases IL-8 expression in monocytes *in vitro* and/or *in vivo*;
- d) induces or increases TNF $\alpha$  expression in macrophages and/or dendritic cells *in vitro* and/or *in vivo*;
- e) induces neutrophil-mediated phagocytosis, for example, of tumor cells *in vitro* and/or *in vivo*;
- o) increases neutrophil-mediated tumor cell clearance *in vivo*;
- p) increases TREM2 expression on macrophages *in vitro* and/or *in vivo*;
- q) increases viability of macrophages *in vitro* and/or *in vivo*, alone and/or in combination with an agonist anti-TREM2 antibody; and
- f) increases viability of dendritic cells *in vitro* and/or *in vivo*.

**[0005]** In one aspect, the present disclosure refers to an isolated antibody that binds to human SIRP $\beta$ 1, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises (a) HVR-H1 comprising an amino acid sequence of an HVR-H1 shown in Table 4 and/or Table 9; (b) HVR-H2 comprising an amino acid sequence of an HVR-H2 shown in Table 4 and/or Table 9; (c) HVR-H3 comprising an amino acid sequence of an HVR-H3 shown in Table 4 and/or Table 9; (d) HVR-L1 comprising an amino acid sequence of an HVR-L1 shown in Table 3 and/or Table 8; (e) HVR-L2 comprising an amino acid sequence of an HVR-L2 shown in Table 3 and/or Table 8; and (f) HVR-L3 comprising an amino acid sequence of an HVR-L3 shown in Table 3 and/or Table 8. In some examples, the heavy chain variable region comprises one, two, three or four framework regions selected from VH FR1, VH FR2, VH FR3, and

VH FR4 shown in Table 6. In some examples, the light chain variable region comprises one, two, three or four framework regions selected from VL FR1, VL FR2, VL FR3, and VL FR4 shown in Table 5.

[0006] In some examples, the antibody comprises HVR-H1, HVR-H2, HVR-H2, HVR-L1, HVR-L2, and HVR-L3 of an antibody selected from SB-1, SB-2, SB-3, SB-4, SB-5, SB-6, SB-7, SB-8, SB-9, SB-10, SB-11, SB-12, SB-13, SB-14, SB-15, SB-16, SB-17, SB-18, SB-19, SB-20, SB-21, SB-22, SB-23, SB-24, SB-25, SB-26, SB-27, SB-28, SB-29, SB-30, SB-31, SB-32, SB-33, SB-34, SB-35, SB-36, SB-37, SB-38, SB-39, SB-40, SB-41, SB-42, SB-43, SB-44, SB-45, SB-46, SB-47, SB-48, SB-49, SB-50, SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21 (shown in Tables 3, 4, 8, and 9). In some examples, the antibody comprises a heavy chain variable region comprising an amino acid sequence at least 90%, at least 95%, at least 97%, or at least 99% identical to a sequence selected from SEQ ID NOs: 268, 270, 272, 274, 276, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 309, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, 361, 363, 365, 366, 367, 368, 369, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, or 382. In some examples, the antibody comprises a heavy chain variable region selected from SEQ ID NOs: 268, 270, 272, 274, 276, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 309, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, 361, 363, 365, 366, 367, 368, 369, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, or 382. In some examples, the antibody comprises a light chain variable region comprising an amino acid sequence at least 90%, at least 95%, at least 97%, or at least 99% identical to a sequence selected from SEQ ID NOs: 267, 269, 271, 273, 275, 277, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, 302, 304, 306, 308, 310, 312, 314, 316, 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, 360, 362, 364, or 370. In some examples, the antibody comprises a light chain variable region selected from SEQ ID NOs: 267, 269, 271, 273, 275, 277, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, 302, 304, 306, 308, 310, 312, 314, 316, 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, 360, 362, 364, or 370. In some examples, the antibody comprises a heavy chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the heavy chain variable region, and a light chain variable region 90%, at least 95%, at least 97%, or at least 99% identical to the light chain variable region, of an antibody selected from SB-1, SB-2, SB-3, SB-4, SB-5, SB-6, SB-7, SB-8, SB-9, SB-10, SB-11, SB-12, SB-13, SB-14, SB-15, SB-16, SB-17, SB-18, SB-19, SB-20, SB-21, SB-22, SB-23, SB-24, SB-25, SB-26, SB-27, SB-28, SB-29, SB-30, SB-31, SB-32, SB-33, SB-34, SB-35, SB-36, SB-37, SB-38, SB-39, SB-40, SB-41, SB-42, SB-43, SB-44, SB-45, SB-46, SB-47, SB-48, SB-49, SB-50, SB-1-2, SB-

1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21. In some examples, the antibody comprises a heavy chain variable region and a light chain variable region of an antibody selected from SB-1, SB-2, SB-3, SB-4, SB-5, SB-6, SB-7, SB-8, SB-9, SB-10, SB-11, SB-12, SB-13, SB-14, SB-15, SB-16, SB-17, SB-18, SB-19, SB-20, SB-21, SB-22, SB-23, SB-24, SB-25, SB-26, SB-27, SB-28, SB-29, SB-30, SB-31, SB-32, SB-33, SB-34, SB-35, SB-36, SB-37, SB-38, SB-39, SB-40, SB-41, SB-42, SB-43, SB-44, SB-45, SB-46, SB-47, SB-48, SB-49, SB-50, SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21.

**[0007]** In some examples, the antibody comprises HVR-H1, HVR-H2, HVR-H2, HVR-L1, HVR-L2, and HVR-L3 of an antibody selected from SB-1, SB-2, SB-3, SB-4, SB-5, SB-6, SB-7, SB-8, SB-9, SB-14, SB-28, SB-39, SB-40, SB-49, SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21 (shown in Tables 3, 4, 8, and 9). In some examples, the antibody comprises a heavy chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the heavy chain variable region of an antibody selected from SB-1, SB-2, SB-3, SB-4, SB-5, SB-6, SB-7, SB-8, SB-9, SB-14, SB-28, SB-39, SB-40, SB-49, SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21. In some examples, the antibody comprises a heavy chain variable region of an antibody selected from SB-1, SB-2, SB-3, SB-4, SB-5, SB-6, SB-7, SB-8, SB-9, SB-14, SB-28, SB-39, SB-40, SB-49, SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21. In some examples, the antibody comprises a light chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the light chain variable region of an antibody selected from SB-1, SB-2, SB-3, SB-4, SB-5, SB-6, SB-7, SB-8, SB-9, SB-14, SB-28, SB-39, SB-40, SB-49, SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21. In some examples, the antibody comprises a light chain variable region of an antibody selected from SB-1, SB-2, SB-3, SB-4, SB-5, SB-6, SB-7, SB-8, SB-9, SB-14, SB-28, SB-39, SB-40, SB-49, SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21. In some examples, the antibody comprises a heavy chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the heavy chain variable region, and a light chain variable region 90%, at least 95%, at least 97%, or at least 99% identical to the light chain variable region, of an antibody selected from SB-1, SB-2, SB-3, SB-4, SB-5, SB-6, SB-7, SB-8, SB-9, SB-14, SB-28, SB-39, SB-40, SB-49, SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-

40-18, SB-40-19, SB-40-20, and SB-40-21. In some examples, the antibody comprises a heavy chain variable region and a light chain variable region of an antibody selected from SB-1, SB-2, SB-3, SB-4, SB-5, SB-6, SB-7, SB-8, SB-9, SB-14, SB-28, SB-39, SB-40, SB-49, SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21.

**[0008]** In some examples, the antibody comprises HVR-H1, HVR-H2, HVR-H2, HVR-L1, HVR-L2, and HVR-L3 of an antibody selected from SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21 (shown in Tables 8 and 9). In some examples, the antibody comprises a heavy chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the heavy chain variable region of an antibody selected from SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21. In some examples, the antibody comprises a heavy chain variable region of an antibody selected from SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21. In some examples, the antibody comprises a light chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the light chain variable region of an antibody selected from SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21. In some examples, the antibody comprises a light chain variable region of an antibody selected from SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21. In some examples, the antibody comprises a heavy chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the heavy chain variable region, and a light chain variable region 90%, at least 95%, at least 97%, or at least 99% identical to the light chain variable region, of an antibody selected from SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21. In some examples, the antibody comprises a heavy chain variable region and a light chain variable region of an antibody selected from SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21.

**[0009]** In some examples, the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 80, 228, or 229; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 101, 239, 239, 240, or 241; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 125; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 383; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 16; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 31. In some examples, the antibody comprises a heavy chain variable

region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 366, 367, 368, or 369. In some examples, the antibody comprises a light chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 267. In some examples, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 366, 367, 368, or 369. In some examples, the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 267.

**[0010]** In some examples, the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 81, 99, 230, 231, or 232; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 102, 242, 243, 244, or 245; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 126 or 253; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 383; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 16; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 32. In some examples, the antibody comprises a heavy chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 371, 372, 373, 374, or 375. In some examples, the antibody comprises a light chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 269 or 370. In some examples, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 371, 372, 373, 374, or 375. In some examples, the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 269 or 370. In some examples, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 371, 372, or 373 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 370; or a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 374 or 375 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 269.

**[0011]** In some examples, the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 85, 233, or 234; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 107, 246, 247, or 248; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 131 or 254; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 383; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 19; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 37. In some examples, the antibody comprises a heavy chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 376, 377, or 378. In some examples, the antibody comprises a light chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 280. In some examples, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 376, 377, or 378. In

some examples, the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 280.

**[0012]** In some examples, the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 97, 235, 236, or 237; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 121, 249, 250, 251, or 252; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 163; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 2; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 22; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 69. In some examples, the antibody comprises a heavy chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 379, 380, 381, or 382. In some examples, the antibody comprises a light chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 344. In some examples, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 379, 380, 381, or 382. In some examples, the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 344.

**[0013]** In some examples, the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 229; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 239; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 125; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 383; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 16; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 31. In some examples, the antibody comprises a heavy chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 367. In some examples, the antibody comprises a light chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 267. In some examples, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 367. In some examples, the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 267.

**[0014]** In some examples, the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 231; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 243; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 126; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 383; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 16; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 32. In some examples, the antibody comprises a heavy chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 372. In some examples, the antibody comprises a light chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 370. In

some examples, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 372. In some examples, the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 270.

**[0015]** In some examples, the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 233; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 246; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 131; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 383; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 19; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 37. In some examples, the antibody comprises a heavy chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 376. In some examples, the antibody comprises a light chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 280. In some examples, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 376. In some examples, the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 280.

**[0016]** In some examples, the antibody is a monoclonal antibody. In some examples, the antibody is of the IgG class, the IgM class, or the IgA class. In some examples, the antibody is of the IgG class and has an IgG1, IgG2, or IgG4 isotype. In some examples, the antibody has an IgG1 isotype. In some examples, the antibody comprises a E430G substitution and a P331S substitution according to EU numbering.

**[0017]** In some examples, the antibody is an antibody fragment. In some examples, the fragment is a Fab, Fab', Fab'-SH, F(ab')<sub>2</sub>, Fv or scFv fragment.

**[0018]** In some examples, the antibody has an affinity ( $K_D$ ) for human SIRPβ1 isoform 1 of 0.1 nM to 50 nM, or 0.5 nM to 10 nM, or 0.5 nM to 5 nM. In some examples, affinity is measured using a ForteBio Octet<sup>®</sup> system.

**[0019]** In some examples, the antibody recognizes a first and a second antigen, wherein the first antigen is SIRPβ1 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), and diphtheria toxin receptor;
- (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.

**[0020]** In some examples, an isolated antibody that binds to human SIRPβ1 is provided, wherein the antibody competes with one or more antibodies provided herein for binding to human SIRPβ1 isoform 1. In some examples, an isolated antibody that binds to human SIRPβ1 is provided, wherein the antibody binds essentially the same or overlapping SIRPβ1 isoform 1 epitope as one or more antibodies provided herein. In one aspect, the present disclosure refers to an isolated antibody that binds to human SIRPβ1, wherein the antibody competes with one or more antibodies disclosed herein for binding to human SIRPβ1 isoform 1, and/or wherein the antibody binds essentially the same or overlapping SIRPβ1 isoform 1 epitope as one or more antibodies as disclosed herein.

**[0021]** In one aspect, the present disclosure refers to an isolated nucleic acid comprising a nucleic acid sequence encoding the antibody as disclosed herein. In some examples, an isolated nucleic acid is provided, comprising a nucleic acid sequence encoding an anti-SIRPβ1 antibody provided herein. In one aspect, the present disclosure refers to a vector comprising the nucleic acid as disclosed herein. In some examples, an isolated host cell is provided, comprising the vector. In some examples, an isolated host cell is provided that expresses an anti-SIRPβ1 antibody provided herein. In one aspect, the present disclosure refers to an isolated host cell comprising the vector as disclosed herein, wherein the host cell expresses the antibody as disclosed herein. In some examples, methods of producing an antibody that binds to human SIRPβ1 are provided, comprising culturing a host cell that expresses an anti-SIRPβ1 antibody provided herein so that the antibody is produced. In some examples, the method further comprises recovering the antibody produced by the cell. In one aspect, the present disclosure refers to a method of producing an antibody that binds to human SIRPβ1, comprising culturing the cell as disclosed herein so that the antibody is produced, optionally further comprising recovering the antibody produced by the cell.

**[0022]** In one aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody as disclosed herein and a pharmaceutically acceptable carrier. In some examples, a pharmaceutical composition is provided, comprising an anti-SIRPβ1 antibody provided herein and a pharmaceutically acceptable carrier.

**[0023]** In some examples, a method of treating cancer is provided, comprising administering to an individual in need thereof a therapeutically effective amount of an anti-SIRPβ1 antibody provided herein. In some examples, the cancer is selected from selected from sarcoma, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal pelvis cancer, leukemia, lung cancer, small cell lung cancer, melanoma, lymphoma, pancreatic

cancer, prostate cancer, ovarian cancer, and fibrosarcoma, glioblastoma multiforme; renal clear cell carcinoma; adrenocortical carcinoma; bladder urothelial carcinoma, diffuse large B-cell lymphoma, lung adenocarcinoma; pancreatic adenocarcinoma, renal cell cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, indolent B cell lymphoma, aggressive B cell lymphoma, T cell lymphoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, myelodysplastic syndromes, myeloproliferative neoplasms, breast invasive carcinoma, cervical squamous cell carcinoma, endocervical adenocarcinoma, cholangiocarcinoma, colon adenocarcinoma, diffuse large B-cell lymphoma, esophageal carcinoma, head and neck squamous cell carcinoma, kidney chromophobe, renal papillary cell carcinoma, lower grade glioma, hepatocellular carcinoma, lung squamous cell carcinoma, mesothelioma, ovarian serous cystadenocarcinoma, pancreatic adenocarcinoma, pheochromocytoma and paraganglioma, prostate adenocarcinoma, rectal adenocarcinoma, cutaneous melanoma, stomach adenocarcinoma, testicular germ cell tumors, thyroid carcinoma, thymoma, uterine corpus endometrial carcinoma, uterine carcinosarcoma, and uveal melanoma.

**[0024]** In some examples, a method of treatment further comprises administering a therapeutic agent that inhibits or agonizes PD1, PDL1, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, CTLA4, PD-L2, B7-H3, B7-H4, HVEM, LIGHT, BTLA, CD30, TIGIT, VISTA, KIR, GAL9, TIM1, TIM3, TIM4, A2AR, LAG3, DR-5, CD2, CD5, CD39, or CD73. In some examples, a method of treatment further comprises administering to the individual at least one antibody that specifically binds to an inhibitory checkpoint molecule, and/or one or more standard or investigational anti-cancer therapies.

**[0025]** In some examples, a method of treatment further comprises administering at least one antibody that specifically binds to an inhibitory checkpoint molecule in combination with the anti-SIRPA antibody. In some examples, the at least one antibody that specifically binds to an inhibitory checkpoint molecule is selected from an anti-PD-L1 antibody, an anti-CTLA4 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-TIM-1 antibody, an anti-TIM3 antibody, an anti-TIM-4 antibody, an anti-A2AR antibody, an anti-CD39 antibody, an anti-CD73 antibody, an anti-LAG-3 antibody, an anti-phosphatidylserine antibody, an anti-CD27 antibody, an anti-CD30 antibody, an anti-TNF $\alpha$  antibody, an anti-CD33 antibody, an anti-Siglec-5 antibody, an anti-Siglec-7 antibody, an anti-Siglec-9 antibody, an anti-Siglec-11 antibody, an antagonistic anti-TREM1 antibody, an

antagonistic anti-TREM2 antibody, an anti-TIGIT antibody, an anti-VISTA antibody, an anti-CD2 antibody, an anti-CD5 antibody, and any combination thereof.

**[0026]** In some examples, a method of treatment further comprises administering one or more standard or investigational anti-cancer therapies selected from radiotherapy, cytotoxic chemotherapy, targeted therapy, imatinib therapy, trastuzumab therapy, etanercept therapy, adoptive cell transfer (ACT) therapy, chimeric antigen receptor T cell transfer (CAR-T) therapy, vaccine therapy, and cytokine therapy.

**[0027]** In some examples, a method of treatment further comprises administering to the individual at least one antibody that specifically binds to an inhibitory cytokine. In some examples, 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.

**[0028]** In some examples, a method of treatment further comprises administering to the individual at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein. In some examples, 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 agonistic anti-TREM1 antibody, an agonistic anti-TREM2 antibody, an agonist anti-CD137/4-1BB antibody, an agonist anti-CD27 antibody, an agonist anti-glucocorticoid-induced TNFR-related protein GITR antibody, an agonist anti-CD30 antibody, an agonist anti-BTLA antibody, an agonist anti-HVEM antibody, an agonist anti-CD2 antibody, an agonist anti-CD5 antibody, and any combination thereof.

**[0029]** In some examples, a method of treatment further comprises administering to the individual at least one stimulatory cytokine. In some examples, the at least one stimulatory cytokine is selected from IFN- $\alpha$ 4, IFN- $\beta$ , IL-1 $\beta$ , TNF- $\alpha$ , IL-6, IL-8, CRP, IL-20 family members, LIF, IFN- $\gamma$ , OSM, CNTF, GM-CSF, IL-11, IL-12, IL-15, IL-17, IL-18, IL-23, CXCL10, IL-33, MCP-1, MIP-1-beta, and any combination thereof.

**[0030]** In some examples, use of an anti-SIRP $\beta$ 1 antibody provided herein for the preparation of a medicament is provided. In some examples, the medicament is for treating cancer. In some examples, an anti-SIRP $\beta$ 1 antibody provided herein is provided for treating cancer. In one aspect, the present disclosure refers to use of an antibody as disclosed herein in the preparation of a medicament for treating cancer in an individual, optionally wherein the cancer is selected from sarcoma, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal pelvis cancer, leukemia, lung cancer, small cell lung cancer, melanoma, lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, and fibrosarcoma, glioblastoma multiforme; renal clear cell carcinoma; adrenocortical carcinoma; bladder urothelial carcinoma, diffuse large B-cell lymphoma, lung adenocarcinoma; pancreatic adenocarcinoma, renal cell cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, indolent B cell lymphoma, aggressive B cell lymphoma, T cell lymphoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, myelodysplastic syndromes, myeloproliferative neoplasms, breast invasive carcinoma, cervical squamous cell carcinoma, endocervical adenocarcinoma, cholangiocarcinoma, colon adenocarcinoma, diffuse large B-cell lymphoma, esophageal carcinoma, head and neck squamous cell carcinoma, kidney chromophobe, renal papillary cell carcinoma, lower grade glioma, hepatocellular carcinoma, lung squamous cell carcinoma, mesothelioma, ovarian serous cystadenocarcinoma, pancreatic adenocarcinoma, pheochromocytoma and paraganglioma, prostate adenocarcinoma, rectal adenocarcinoma, cutaneous melanoma, stomach adenocarcinoma, testicular germ cell tumors, thyroid carcinoma, thymoma, uterine corpus endometrial carcinoma, uterine carcinosarcoma, and uveal melanoma.

**[0031]** In some examples, a method of treating a neurodegenerative disease or disorder is provided, comprising administering to an individual in need thereof a therapeutically effective amount of an anti-SIRP $\beta$ 1 antibody provided herein. In some examples, the neurodegenerative disease or disorder is selected from dementia, frontotemporal dementia, progressive supranuclear palsy, Alzheimer's disease, vascular dementia, Nasu-Hakola disease, cognitive

deficit, memory loss, seizures, retinal dystrophy, amyotrophic lateral sclerosis, traumatic brain injury, a spinal cord injury, stroke, Parkinson's disease, acute disseminated encephalomyelitis, retinal degeneration, age related macular degeneration, glaucoma, multiple sclerosis.

[0032] In some examples, use of an anti-SIRP $\beta$ 1 antibody provided herein for the preparation of a medicament for treating a neurodegenerative disease or disorder is provided. In some examples, the neurodegenerative disease or disorder is selected from dementia, frontotemporal dementia, progressive supranuclear palsy, Alzheimer's disease, vascular dementia, Nasu-Hakola disease, cognitive deficit, memory loss, seizures, retinal dystrophy, amyotrophic lateral sclerosis, traumatic brain injury, a spinal cord injury, stroke, Parkinson's disease, acute disseminated encephalomyelitis, retinal degeneration, age related macular degeneration, glaucoma, multiple sclerosis. In one aspect, the present disclosure refers to use of the antibody as disclosed herein in the preparation of a medicament for treating a neurodegenerative disease or disorder in an individual, optionally wherein the neurodegenerative disease or disorder is selected from dementia, frontotemporal dementia, progressive supranuclear palsy, Alzheimer's disease, vascular dementia, Nasu-Hakola disease, cognitive deficit, memory loss, seizures, retinal dystrophy, amyotrophic lateral sclerosis, traumatic brain injury, a spinal cord injury, stroke, Parkinson's disease, acute disseminated encephalomyelitis, retinal degeneration, age related macular degeneration, glaucoma, multiple sclerosis. In some examples, an anti-SIRP $\beta$ 1 antibody provided herein for use in treating a neurodegenerative disease or disorder is provided. In some examples, the neurodegenerative disease or disorder is selected from dementia, frontotemporal dementia, progressive supranuclear palsy, Alzheimer's disease, vascular dementia, Nasu-Hakola disease, cognitive deficit, memory loss, seizures, retinal dystrophy, amyotrophic lateral sclerosis, traumatic brain injury, a spinal cord injury, stroke, Parkinson's disease, acute disseminated encephalomyelitis, retinal degeneration, age related macular degeneration, glaucoma, multiple sclerosis.

[0033] It is to be understood that one, some, or all of the properties of the various examples described herein may be combined to form other examples of the present disclosure. These and other aspects of the disclosure will become apparent to one of skill in the art. These and other examples of the disclosure are further described by the detailed description that follows.

#### **BRIEF DESCRIPTION OF THE DRAWINGS**

[0034] **FIG. 1A** shows an alignment of the amino acid sequences of SIRP $\beta$ 1 isoform 1 (SEQ ID NO: 1; Uniprot Accession No. O00241) and SIRP $\beta$ 1 isoform 3 (SEQ ID NO: 384; Uniprot Accession No. Q5TFQ8). **FIG. 1B** shows an alignment of the amino acid sequences of SIRP $\beta$ 1 isoform 1 (SEQ ID NO: 1) with SIRP $\alpha$  (SEQ ID NO: 385; Uniprot Accession No. P78324), which shows high homology within the extracellular domains.

[0035] **FIG. 2** shows an alignment of the amino acid sequences of human SIRP $\beta$ 1 isoform 1 (SEQ ID NO: 1) and mouse SIRP $\beta$ 1 (SEQ ID NO: 386; Uniprot Accession No. Q8BFX8).

[0036] **FIG. 3A-3B** shows induction of human SIRP $\beta$ 1-dependent luciferase expression in a cell-based reporter assay. Cells were stimulated with plate-bound anti-SIRP $\beta$ 1 antibodies (3A) or anti-SIRP $\alpha$  (SA-9C2) (3B) or human IgG1 isotype control. Results are expressed as fold over background. The background level is set to 1 on y-axis.

[0037] **FIG. 4A** shows the expression pattern of two DAP12-associated receptors, SIRP $\beta$ 1 and TREM1, on human monocytes. Shaded histograms represent background fluorescence from isotype

## CLAIMS

What is claimed is:

1. An isolated antibody that binds to human SIRP $\beta$ 1, wherein the antibody has at least one, at least two, at least three, at least four, or at least five properties selected from:
  - a) binds to human SIRP $\beta$ 1 isoform 1, but does not bind to human SIRP $\alpha$ ;
  - b) binds to human SIRP $\beta$ 1 isoform 1, but does not bind to human SIRP $\gamma$ ;
  - c) binds to human SIRP $\beta$ 1 isoform 1, but does not bind to human SIRP $\beta$ 1 isoform 3;
  - d) binds to human SIRP $\beta$ 1 isoform 1, but does not bind to mouse SIRP $\beta$ 1;
  - e) binds to human SIRP $\beta$ 1 isoform 1, but does not bind to cynomolgus monkey SIRP $\beta$ 1 isoform 1;
  - f) agonizes SIRP $\beta$ 1 activity on CD14-positive monocytes *in vitro* and/or *in vivo*;
  - g) induces or increases respiratory burst in immune cells, such as neutrophils and/or monocytes *in vitro* and/or *in vivo*;
  - h) induces or increases IL-8 expression in monocytes *in vitro* and/or *in vivo*;
  - i) induces or increases TNF $\alpha$  expression in macrophages and/or dendritic cells *in vitro* and/or *in vivo*;
  - j) induces neutrophil-mediated phagocytosis, for example, of tumor cells *in vitro* and/or *in vivo*;
  - k) increases neutrophil-mediated tumor cell clearance *in vivo*;
  - l) increases TREM2 expression on macrophages *in vitro* and/or *in vivo*;
  - m) increases viability of macrophages *in vitro* and/or *in vivo*, alone and/or in combination with an agonist anti-TREM2 antibody; and
  - n) increases viability of dendritic cells *in vitro* and/or *in vivo*.
2. The isolated antibody of claim 1, wherein the antibody binds to human SIRP $\beta$ 1 isoform 1, but does not bind to human SIRP $\alpha$  or human SIRP $\beta$ 1 isoform 3; or wherein the antibody binds to human SIRP $\beta$ 1 isoform 1, but does not bind to human SIRP $\alpha$ , SIRP $\gamma$ , or human SIRP $\beta$ 1 isoform 3.
3. The isolated antibody of claim 1 or claim 2, wherein the antibody has at least one, at least two, or at least three properties selected from:
  - a) agonizes SIRP $\beta$ 1 activity on CD14-positive monocytes *in vitro* and/or *in vivo*;
  - b) induces or increases respiratory burst in immune cells, such as neutrophils and/or monocytes *in vitro* and/or *in vivo*;
  - c) induces or increases IL-8 expression in monocytes *in vitro* and/or *in vivo*;
  - d) induces or increases TNF $\alpha$  expression in macrophages and/or dendritic cells *in vitro* and/or *in vivo*;
  - e) induces neutrophil-mediated phagocytosis, for example, of tumor cells *in vitro* and/or *in vivo*;

- o) increases neutrophil-mediated tumor cell clearance *in vivo*;
  - p) increases TREM2 expression on macrophages *in vitro* and/or *in vivo*;
  - q) increases viability of macrophages *in vitro* and/or *in vivo*, alone and/or in combination with an agonist anti-TREM2 antibody; and
  - f) increases viability of dendritic cells *in vitro* and/or *in vivo*.
4. An isolated antibody that binds to human SIRPβ1, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises (a) HVR-H1 comprising an amino acid sequence of an HVR-H1 shown in Table 4 and/or Table 9; (b) HVR-H2 comprising an amino acid sequence of an HVR-H2 shown in Table 4 and/or Table 9; (c) HVR-H3 comprising an amino acid sequence of an HVR-H3 shown in Table 4 and/or Table 9; (d) HVR-L1 comprising an amino acid sequence of an HVR-L1 shown in Table 3 and/or Table 8; (e) HVR-L2 comprising an amino acid sequence of an HVR-L2 shown in Table 3 and/or Table 8; and (f) HVR-L3 comprising an amino acid sequence of an HVR-L3 shown in Table 3 and/or Table 8.
5. The antibody of claim 4, wherein the heavy chain variable region comprises one, two, three or four framework regions selected from VH FR1, VH FR2, VH FR3, and VH FR4 shown in Table 6, and/or wherein the light chain variable region comprises one, two, three or four framework regions selected from VL FR1, VL FR2, VL FR3, and VL FR4 shown in Table 5.
6. The antibody of any one of claims 1-5, wherein the antibody comprises HVR-H1, HVR-H2, HVR-H2, HVR-L1, HVR-L2, and HVR-L3 of an antibody selected from SB-1, SB-2, SB-3, SB-4, SB-5, SB-6, SB-7, SB-8, SB-9, SB-10, SB-11, SB-12, SB-13, SB-14, SB-15, SB-16, SB-17, SB-18, SB-19, SB-20, SB-21, SB-22, SB-23, SB-24, SB-25, SB-26, SB-27, SB-28, SB-29, SB-30, SB-31, SB-32, SB-33, SB-34, SB-35, SB-36, SB-37, SB-38, SB-39, SB-40, SB-41, SB-42, SB-43, SB-44, SB-45, SB-46, SB-47, SB-48, SB-49, SB-50, SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21 (shown in Tables 3, 4, 8, and 9).
7. The antibody of any one of claims 1-6, wherein the antibody comprises a heavy chain variable region comprising an amino acid sequence at least 90%, at least 95%, at least 97%, or at least 99% identical to a sequence selected from SEQ ID NOs: 268, 270, 272, 274, 276, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 309, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, 361, 363, 365, 366, 367, 368, 369, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, or 382; and/or wherein the antibody comprises a light chain variable region comprising an amino acid sequence at least 90%, at least 95%, at least 97%, or at least 99% identical to a sequence selected from SEQ ID NOs: 267, 269, 271, 273, 275, 277, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, 302,

304, 306, 308, 310, 312, 314, 316, 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, 360, 362, 364, or 370.

8. The antibody of any one of claims 1-7, wherein the antibody comprises a heavy chain variable region selected from SEQ ID NOs: 268, 270, 272, 274, 276, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 309, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, 361, 363, 365, 366, 367, 368, 369, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, or 382; and/or wherein the antibody comprises a light chain variable region selected from SEQ ID NOs: 267, 269, 271, 273, 275, 277, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, 302, 304, 306, 308, 310, 312, 314, 316, 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, 360, 362, 364, or 370.

9. The antibody of any one of claims 1-5, wherein the antibody comprises HVR-H1, HVR-H2, HVR-H2, HVR-L1, HVR-L2, and HVR-L3 of an antibody selected from SB-1, SB-2, SB-3, SB-4, SB-5, SB-6, SB-7, SB-8, SB-9, SB-14, SB-28, SB-39, SB-40, SB-49, SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21 (shown in Tables 3, 4, 8, and 9).

10. The antibody of claim 9, wherein the antibody comprises a heavy chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the heavy chain variable region of an antibody selected from SB-1, SB-2, SB-3, SB-4, SB-5, SB-6, SB-7, SB-8, SB-9, SB-14, SB-28, SB-39, SB-40, SB-49, SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21; and/or wherein the antibody comprises a light chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the light chain variable region of an antibody selected from SB-1, SB-2, SB-3, SB-4, SB-5, SB-6, SB-7, SB-8, SB-9, SB-14, SB-28, SB-39, SB-40, SB-49, SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21.

11. The antibody of claim 9 or claim 10, wherein the antibody comprises a heavy chain variable region of an antibody selected from SB-1, SB-2, SB-3, SB-4, SB-5, SB-6, SB-7, SB-8, SB-9, SB-14, SB-28, SB-39, SB-40, SB-49, SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21; and/or wherein the antibody comprises a light chain variable region of an antibody selected from SB-1, SB-2, SB-3, SB-4, SB-5, SB-6, SB-7, SB-8, SB-9, SB-14, SB-28, SB-39, SB-40, SB-49, SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21.

12. The antibody of any one of claims 1-5, wherein the antibody comprises HVR-H1, HVR-H2, HVR-H2, HVR-L1, HVR-L2, and HVR-L3 of an antibody selected from SB-1-2, SB-1-3, SB-1-4,

SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21 (shown in Tables 8 and 9).

13. The antibody of claim 12, wherein the antibody comprises a heavy chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the heavy chain variable region of an antibody selected from SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21; and/or wherein the antibody comprises a light chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the light chain variable region of an antibody selected from SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21.

14. The antibody of claim 12 or claim 13, wherein the antibody comprises a heavy chain variable region of an antibody selected from SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21; and/or wherein the antibody comprises a light chain variable region of an antibody selected from SB-1-2, SB-1-3, SB-1-4, SB-1-5, SB-2-7, SB-2-8, SB-2-9, SB-2-10, SB-2-11, SB-8-13, SB-8-14, SB-8-15, SB-8-16, SB-40-18, SB-40-19, SB-40-20, and SB-40-21.

15. The antibody of any one of claims 1-5, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 80, 228, or 229; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 101, 239, 239, 240, or 241; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 125; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 383; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 16; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 31.

16. The antibody of claim 15, wherein the antibody comprises a heavy chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 366, 367, 368, or 369; and/or wherein the antibody comprises a light chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 267.

17. The antibody of claim 15 or 16, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 366, 367, 368, or 369; and/or wherein the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 267.

18. The antibody of any one of claims 1-5, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 81, 99, 230, 231, or 232; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 102, 242, 243, 244, or 245; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 126 or 253; (d) HVR-L1 comprising the amino

acid sequence of SEQ ID NO: 383; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 16; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 32.

19. The antibody of claim 18, wherein the antibody comprises a heavy chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 371, 372, 373, 374, or 375; and/or wherein the antibody comprises a light chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 269 or 370.

20. The antibody of claim 18 or 19, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 371, 372, 373, 374, or 375; and/or wherein the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 269 or 370.

21. The antibody of any one of claims 1-5, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 85, 233, or 234; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 107, 246, 247, or 248; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 131 or 254; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 383; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 19; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 37.

22. The antibody of claim 21, wherein the antibody comprises a heavy chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 376, 377, or 378; and/or wherein the antibody comprises a light chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 280.

23. The antibody of claim 21 or 22, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 376, 377, or 378; and/or wherein the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 280.

24. The antibody of any one of claims 1-5, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 97, 235, 236, or 237; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 121, 249, 250, 251, or 252; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 163; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 2; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 22; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 69.

25. The antibody of claim 24, wherein the antibody comprises a heavy chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 379, 380, 381, or 382; and/or wherein the antibody comprises a light chain variable

region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 344.

26. The antibody of claim 24 or 25, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 379, 380, 381, or 382; and/or wherein the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 344.

27. The antibody of any one of claims 1-5, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 229; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 239; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 125; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 383; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 16; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 31.

28. The antibody of claim 27, wherein the antibody comprises a heavy chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 367; and/or wherein the antibody comprises a light chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 267.

29. The antibody of claim 26 or 27, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 367; and/or wherein the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 267.

30. The antibody of any one of claims 1-5, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 231; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 243; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 126; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 383; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 16; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 32.

31. The antibody of claim 30, wherein the antibody comprises a heavy chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 372; and/or wherein the antibody comprises a light chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 370.

32. The antibody of claim 30 or 31, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 372; and/or wherein the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 270.

33. The antibody of any one of claims 1-5, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 233; (b) HVR-H2 comprising the amino acid

sequence of SEQ ID NO: 246; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 131; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 383; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 19; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 37.

34. The antibody of claim 33, wherein the antibody comprises a heavy chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 376; and/or wherein the antibody comprises a light chain variable region that is at least 90%, at least 95%, at least 97%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 280.

35. The antibody of claim 33 or 34, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 376; and/or wherein the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 280.

36. The antibody of any one of claims 1-35, wherein the antibody is a monoclonal antibody, and/or wherein the antibody is of the IgG class, the IgM class, or the IgA class.

37. The antibody of claim 36, wherein the antibody is of the IgG class and has an IgG1, IgG2, or IgG4 isotype.

38. The antibody of claim 37, wherein the antibody has an IgG1 isotype, optionally comprising a E430G substitution and a P331S substitution according to EU numbering.

39. The antibody of any one of claims 1-38, wherein the antibody is an antibody fragment, optionally comprising a Fab, Fab', Fab'-SH, F(ab')<sub>2</sub>, Fv or scFv fragment.

40. The antibody of any one of claims 1-39, wherein the antibody has an affinity (K<sub>D</sub>) for human SIRPβ1 isoform 1 of 0.1 nM to 50 nM, or 0.5 nM to 10 nM, or 0.5 nM to 5 nM, optionally wherein affinity is measured using a ForteBio Octet<sup>®</sup> system.

41. The antibody of any one of claims 1-40, wherein the antibody recognizes a first and a second antigen, wherein the first antigen is SIRPβ1 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), and diphtheria toxin receptor;
- (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.

42. An isolated antibody that binds to human SIRP $\beta$ 1, wherein the antibody competes with one or more antibodies of any one of claims 1-41 for binding to human SIRP $\beta$ 1 isoform 1, and/or wherein the antibody binds essentially the same or overlapping SIRP $\beta$ 1 isoform 1 epitope as one or more antibodies of any one of claims 1-41.

43. An isolated nucleic acid comprising a nucleic acid sequence encoding the antibody of any one of the preceding claims.

44. A vector comprising the nucleic acid of claim 43.

45. An isolated host cell comprising the vector of claim 44, wherein the host cell expresses the antibody of any one of claims 1-42.

46. A method of producing an antibody that binds to human SIRP $\beta$ 1, comprising culturing the cell of claim 45 so that the antibody is produced, optionally further comprising recovering the antibody produced by the cell.

47. A pharmaceutical composition comprising the antibody of any one of claims 1-42 and a pharmaceutically acceptable carrier.

48. Use of an antibody of any one of claims 1-42 in the preparation of a medicament for treating cancer in an individual, optionally wherein the cancer is selected from sarcoma, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal pelvis cancer, leukemia, lung cancer, small cell lung cancer, melanoma, lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, and fibrosarcoma, glioblastoma multiforme; renal clear cell carcinoma; adrenocortical carcinoma; bladder urothelial carcinoma, diffuse large B-cell lymphoma, lung adenocarcinoma; pancreatic adenocarcinoma, renal cell cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, indolent B cell lymphoma, aggressive B cell lymphoma, T cell lymphoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL),

chronic myeloid leukemia (CML), multiple myeloma, myelodysplastic syndromes, myeloproliferative neoplasms, breast invasive carcinoma, cervical squamous cell carcinoma, endocervical adenocarcinoma, cholangiocarcinoma, colon adenocarcinoma, diffuse large B-cell lymphoma, esophageal carcinoma, head and neck squamous cell carcinoma, kidney chromophobe, renal papillary cell carcinoma, lower grade glioma, hepatocellular carcinoma, lung squamous cell carcinoma, mesothelioma, ovarian serous cystadenocarcinoma, pancreatic adenocarcinoma, pheochromocytoma and paraganglioma, prostate adenocarcinoma, rectal adenocarcinoma, cutaneous melanoma, stomach adenocarcinoma, testicular germ cell tumors, thyroid carcinoma, thymoma, uterine corpus endometrial carcinoma, uterine carcinosarcoma, and uveal melanoma.

49. The use of claim 48, wherein the individual is to be administered (a) a therapeutic agent that inhibits or agonizes PD1, PDL1, CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, CTLA4, PD-L2, B7-H3, B7-H4, HVEM, LIGHT, BTLA, CD30, TIGIT, VISTA, KIR, GAL9, TIM1, TIM3, TIM4, A2AR, LAG3, DR-5, CD2, CD5, CD39, or CD73; (b) at least one antibody that specifically binds to an inhibitory checkpoint molecule, and/or (c) one or more standard or investigational anti-cancer therapies optionally wherein the at least one antibody that specifically binds to an inhibitory checkpoint molecule is selected from an anti-PD-L1 antibody, an anti-CTLA4 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-TIM-1 antibody, an anti-TIM3 antibody, an anti-TIM-4 antibody, an anti-A2AR antibody, an anti-CD39 antibody, an anti-CD73 antibody, an anti-LAG-3 antibody, an anti-phosphatidylserine antibody, an anti-CD27 antibody, an anti-CD30 antibody, an anti-TNF $\alpha$  antibody, an anti-CD33 antibody, an anti-Siglec-5 antibody, an anti-Siglec-7 antibody, an anti-Siglec-9 antibody, an anti-Siglec-11 antibody, an antagonistic anti-TREM1 antibody, an antagonistic anti-TREM2 antibody, an anti-TIGIT antibody, an anti-VISTA antibody, an anti-CD2 antibody, an anti-CD5 antibody, and any combination thereof; and wherein the one or more standard or investigational anti-cancer therapies are selected from radiotherapy, cytotoxic chemotherapy, targeted therapy, imatinib therapy, trastuzumab therapy, etanercept therapy, adoptive cell transfer (ACT) therapy, chimeric antigen receptor T cell transfer (CAR-T) therapy, vaccine therapy, and cytokine therapy.

50. The use of claim 48 or claim 49, wherein the individual is to be administered at least one antibody that specifically binds to an inhibitory cytokine optionally selected from an anti-CCL2 antibody, an anti-CSF-1 antibody, an anti-IL-2 antibody, and any combination thereof.

51. The use of any one of claims 48-50, wherein the individual is to be administered at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein optionally selected from an agonist anti-CD40 antibody, an agonist anti-OX40 antibody, an agonist anti-ICOS antibody, an agonist anti-CD28 antibody, an agonistic anti-TREM1 antibody, an agonistic anti-TREM2 antibody, an agonist anti-CD137/4-1BB antibody, an agonist anti-CD27 antibody, an agonist anti-glucocorticoid-induced TNFR-related protein GITR antibody, an agonist anti-CD30 antibody, an agonist anti-BTLA antibody, an

agonist anti-HVEM antibody, an agonist anti-CD2 antibody, an agonist anti-CD5 antibody, and any combination thereof.

52. The use of any one of claims 48-51, wherein the individual is to be further administered at least one stimulatory cytokine optionally selected from IFN- $\alpha$ 4, IFN- $\beta$ , IL-1 $\beta$ , TNF- $\alpha$ , IL-6, IL-8, CRP, IL-20 family members, LIF, IFN- $\gamma$ , OSM, CNTF, GM-CSF, IL-11, IL-12, IL-15, IL-17, IL-18, IL-23, CXCL10, IL-33, MCP-1, MIP-1-beta, and any combination thereof.

53. Use of the antibody of any one of claims 1-42 in the preparation of a medicament for treating a neurodegenerative disease or disorder in an individual, optionally wherein the neurodegenerative disease or disorder is selected from dementia, frontotemporal dementia, progressive supranuclear palsy, Alzheimer's disease, vascular dementia, Nasu-Hakola disease, cognitive deficit, memory loss, seizures, retinal dystrophy, amyotrophic lateral sclerosis, traumatic brain injury, a spinal cord injury, stroke, Parkinson's disease, acute disseminated encephalomyelitis, retinal degeneration, age related macular degeneration, glaucoma, multiple sclerosis.